Meta-analysis of placebo response and subject dropout in placebo-controlled randomized clinical trials for antipsychotics

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Abstract

Schizophrenia treatment has been shifting to resocialization with the emergence of new efficacious antipsychotic drugs. However, even some of the pivotal studies of approved new antipsychotic drugs with proven efficacy had failed due to high placebo response. It was reported that the placebo response in antipsychotic drug trials have increased over time. Also, dropout rates in placebo arms of placebo-controlled randomized clinical trials (RCTs) of antipsychotics were reported to be generally high, and missing data resulting from subject dropout represent a potential source of bias. The aim of this study was to identify the potential factors affecting placebo response and subject dropout by meta-analysis for placebo-controlled RCTs for antipsychotics using Positive and Negative Syndrome Scale (PANSS) focusing on the current methodological change in the handling of missing data and type of antipsychotics for successful future clinical trials.

In the Research 1, recent trends in the degree of placebo response, mean change of PANSS total score in the placebo arm, were investigated based on articles of RCTs for antipsychotics published up to 2016. The potential factors affecting the degree of placebo response, such as study design and operational factors, were analyzed by meta-regression; we conducted the analyses separately for Last Observation Carried Forward (LOCF)-based data and Mixed-effect Models for Repeated Measures (MMRM)-based data. There

was no correlation between the publication year and the mean change of PANSS score in the placebo arm of RCTs of antipsychotics. The number of countries and treatment setting in the MMRM-based data and study duration in the LOCF-based data were significantly associated with placebo response.

In the Research 2, in order to investigate subject dropout, we extracted necessary information from the articles published up to 2018 and investigated the potential factors affecting the degree of subject dropout from clinical trials. In the multivariate meta-regression analysis, publication year of the article, age of patients, and study duration were significantly associated with the subject dropout rate.

It was shown that placebo response in antipsychotics RCTs of recent years had not increased over time and that subject dropout rates had decreased in recent atypical antipsychotics RCTs in our research. In designing placebo-controlled RCTs for antipsychotics, in order to adequately control the degree of placebo response, the number of countries participating in the study and the duration/condition of patient hospitalization during the study should be considered. Also, study design with as short a duration as possible, with due consideration of the mode of action of the new antipsychotics, would decrease subjects' dropout in future placebo-controlled RCTs.

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Abbreviations

AE	Adverse Event
ANCOVA	Analysis of covariance
BPRS	Brief Psychiatric Rating Scale
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDA	U.S. Food and Drug Administration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LOCF	Last Observation Carried Forward
MMRM	Mixed-effect Models for Repeated Measures
NRC	US National Research Council
PANSS	Positive and Negative Syndrome Scale
RCT	Randomized Clinical Trial

1. Introduction

Efficacious new atypical antipsychotic drugs with fewer side effects have been developed and launched since the 1990s, providing new opportunities in schizophrenia treatment not only for symptom control, but also for remission and resocialization [1, 2].

The study design of clinical trials of new antipsychotics is determined in reference to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 guideline "Statistical Principles for Clinical Trials" [3] and E10 guideline "Choice of Control Group and Related Issues in Clinical Trials" [4]. Nation-specific regulatory requirements and ethical concerns related to target patients are also taken into consideration [5, 6]. Consequently, placebo-controlled studies have been largely adopted as pivotal studies in trials for new antipsychotic drugs for schizophrenia.

In the central nervous system (CNS) therapeutic area, only 9% of compounds reaching Phase 1 survived to launch, with about 50% failure in Phase 3 [7, 8]. It was reported that the failure rate of clinical studies was approximately 25% in five programs for schizophrenia drugs that were all eventually approved in the US [9]. The placebo response in antipsychotic drug trials was reported to have increased over time [10-13] and increasing placebo response rates decrease drug-placebo differences and increase the

number of failed trials [13]. In a recent development program of an antipsychotic, which led to its marketing approval, the placebo-controlled randomized clinical trials (RCTs) [14, 15] failed due to high placebo response.

Additionally, high dropout rates of antipsychotics RCTs, which is a potential source of bias and decrease statistical power of RCTs, have been reported in previous studies [16-18]. ICH E9 guideline states that missing values resulting from dropout represent a potential source of bias in clinical trials [3]. Meanwhile, the mean dropout rate in placebo arms of placebo-controlled RCTs of second- and first-generation antipsychotics was 60.2 and 63.3%, respectively [17]. Thus, if placebo-controlled RCTs of antipsychotics fail due to high placebo response and high dropout rates, it would take longer development time, resulting in delay of patients' access to the drug. Preventive methods should be taken to minimize the occurrence of placebo response and subject dropout from studies, particularly in placebo-controlled RCTs of antipsychotics that would be characterized by high placebo response rates and subject dropout rates.

Recently, there have been some changes in the circumstances surrounding RCTs of antipsychotics. First, the type of antipsychotics in RCTs has changed from first-generation (typical) antipsychotics to atypical antipsychotics. Second, the scale of psychiatric symptom assessment has changed; Positive and Negative Syndrome Scale (PANSS),

which is a well-established scale in rating schizophrenia symptoms, is frequently used as a primary measure of efficacy in place of Brief Psychiatric Rating Scale (BPRS) in recent clinical trials [19-21]. Third, the handling of missing data has undergone a significant methodological shift from Last Observation Carried Forward (LOCF) to Mixed-effect Models for Repeated Measures (MMRM), [22-25] which is a particular form of a mixed model analysis[26].

The degree of placebo response and subject dropout in the placebo arm of RCTs of antipsychotics with considerations of those changes have not been evaluated. In considering such a situation, identifying factors that might influence placebo response and subject dropout would assist the planning of design of new clinical trials. In this study, we aimed to identify the potential factors affecting placebo response and subject dropout in RCTs of antipsychotics using a consistent psychiatric symptom assessment scale, PANSS, by a meta-analysis.

2. Research 1

2.1 Background and Objectives

Schizophrenia treatment has been shifting to resocialization with the emergence of efficacious antipsychotic drugs. However, even some of the pivotal studies of approved

new antipsychotic drugs with proven efficacy had failed due to high placebo response. Identifying the potential factors associated with the increase of placebo response in schizophrenia placebo-controlled RCTs under the changes of psychiatric symptom assessment scale and method of the handling of missing data will improve the success rate of placebo-controlled RCTs for potential new antipsychotic drugs and accelerate the development of efficacious new antipsychotic drugs. The aim of this study was to identify the potential factors affecting placebo response by meta-analysis for randomized clinical trials for antipsychotics using Positive and Negative Syndrome Scale (PANSS) focusing on the current methodological change in the handling of missing data [from Last Observation Carried Forward (LOCF) to Mixed-effect Models for Repeated Measures (MMRM)] for successful future clinical trials.

2.2 Methods

2.2.1 Search Strategy

We searched Medline, Embase, Cochrane Central Register of Controlled Trials and PsycINFO using the keywords “Schizophrenia” and “Placebo”, and the following search limits: “Randomized controlled trial”, “Human and Humans”, “Adulthood” and “Publication year up to January 2017” to identify placebo-controlled RCTs for

antipsychotic drugs using PANSS total score as a psychiatric symptom assessment.

2.2.2 Selection Criteria

We excluded clinical trials which were not randomized double-blind placebo-controlled trials, or did not use PANSS total score. Other exclusion criteria included studies for add-on treatments, augmentation treatments or adjunctive medication, studies with cross-over design or non-oral administration, studies for children or adolescents, and studies with stabilization phase by antipsychotic drugs prior to randomization. Also, clinical trials to which neither MMRM nor LOCF was applied or those which had missing values for the analysis were excluded.

2.2.3 Data Extraction

We extracted data or values from the selected articles. We supplementarily referred to FDA (U.S. Food and Drug Administration) medical and statistical reviews, and ClinicalTrials.gov. We defined placebo response as the mean change of PANSS total score from baseline to the last assessment for the primary efficacy in the placebo arm. The values of mean change of PANSS total score by MMRM and/or LOCF were extracted from the selected studies. In addition to the known potential factors of placebo response highlighted in current reports in CNS therapeutic area [11-13, 27], unprecedented potential factors were added and categorized into the following groups:

- Patient factors: diagnosis, severity, mean age at baseline, % male,
- Investigator factor: rater training [28],
- Study design factors: study duration, placebo lead-in, number of treatment arms, placebo randomization rate, regimen, active comparator setting [29], treatment setting,
- Operational factors: number of study sites, number of countries, study period, enrollment speed.

Diagnosis was categorized as either DSM (Diagnostic and Statistical Manual of Mental Disorders)-III-R or DSM-IV-(TR). Severity was defined as the mean PANSS total score at baseline. Rater training was categorized as either studies with rater training or central rating, or studies without mentioning them. Study duration was defined as the treatment period for patients in the study. Placebo lead-in was categorized as either studies with single/double-blind placebo lead-in period, or studies without it. Regimen was categorized as either studies with a fixed dose throughout the study period, or studies with a fixed titration. Active comparator setting was categorized as either studies with active comparators, or those without it. Treatment setting was categorized as either studies requiring hospitalization for the entire duration, or those allowing hospital discharge during the study period according to the investigator's judgement. Study period was

defined as the period from the start to the end of the clinical trial. Enrollment speed was calculated as the total number of randomized patients divided by the number of study sites and study period.

The quality of the included published papers was assessed using Jadad score [30]. Two authors (A.M. and M.K.) assessed independently the selected studies and extracted data. Any disagreements were resolved by discussion between the two authors or consensus with another author (M.N.) as needed.

2.2.4 Data Analyses

Differences between MMRM and LOCF in the mean change of PANSS score in the placebo arm

The differences in the mean change of psychiatric symptom assessment score in the placebo arm between MMRM and LOCF have been reported [22, 31]. We analyzed the differences in the mean change of PANSS total score based on MMRM and LOCF in the placebo arm by applying a paired t-test for six studies that provided both values in order to investigate the possibility that the differences of the mean change between MMRM-based and LOCF-based data affect the meta-analyses. The analysis was performed using StatsDirect version 3.1.1 (StatsDirect Ltd., Altrincham, Cheshire, UK). The result of the analysis confirmed that MMRM-based and LOCF-based data should be analyzed

separately since there was a significant difference in the mean change of PANSS score in the placebo arm between the two methods for six studies for which both MMRM-based and LOCF-based data were available in the present study (supplementary material A1).

Correlation between publication year and mean change of PANSS total score in the placebo arm

We investigated the recent trends in the degree of placebo response by evaluating the sample size weighted correlation between the publication year and the mean change of PANSS total score by either LOCF or MMRM as a primary analysis by using R software version 3.4.0 [32].

Meta-regression analyses

Univariate meta-regression analyses for the potential factors influencing placebo response were performed using random-effects model. A significant association was defined as $p<0.1$ in the univariate analysis. For those factors identified by the univariate analysis, multivariate meta-regression analyses were then performed. These meta-regression analyses were performed separately for either MMRM-based data or LOCF-based data.

The meta-analyses were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [33] and were

performed using R software version 3.4.0 [32].

2.3 Results

2.3.1 Included studies for the analysis

We identified 5,741 articles through the database search. After removing duplicated 2,788 articles, we reviewed 2,953 abstracts and excluded 2,855 articles due to their study design and other reasons. Then, we assessed 98 full-text articles and identified 43 articles with 45 placebo-controlled RCTs using PANSS total score as a psychiatric symptom assessment for the present research. Of the 45 trials, only MMRM was applied in 10 trials, only LOCF was applied in 27 trials, both MMRM and LOCF were applied in 6 trials, and neither was applied in 2 trials; these 2 trials were then excluded from the analysis (Figure1). 28 LOCF-based trials and 15 MMRM-based trials with were included in our mete-regression analyses. The characteristics of the 45 identified placebo-controlled RCTs are shown in Table 1 [34-62, 14, 63-71, 15, 72-74].

The mean Jadad score for the included published trials was 4.3, and they were considered to have adequate methodological quality.

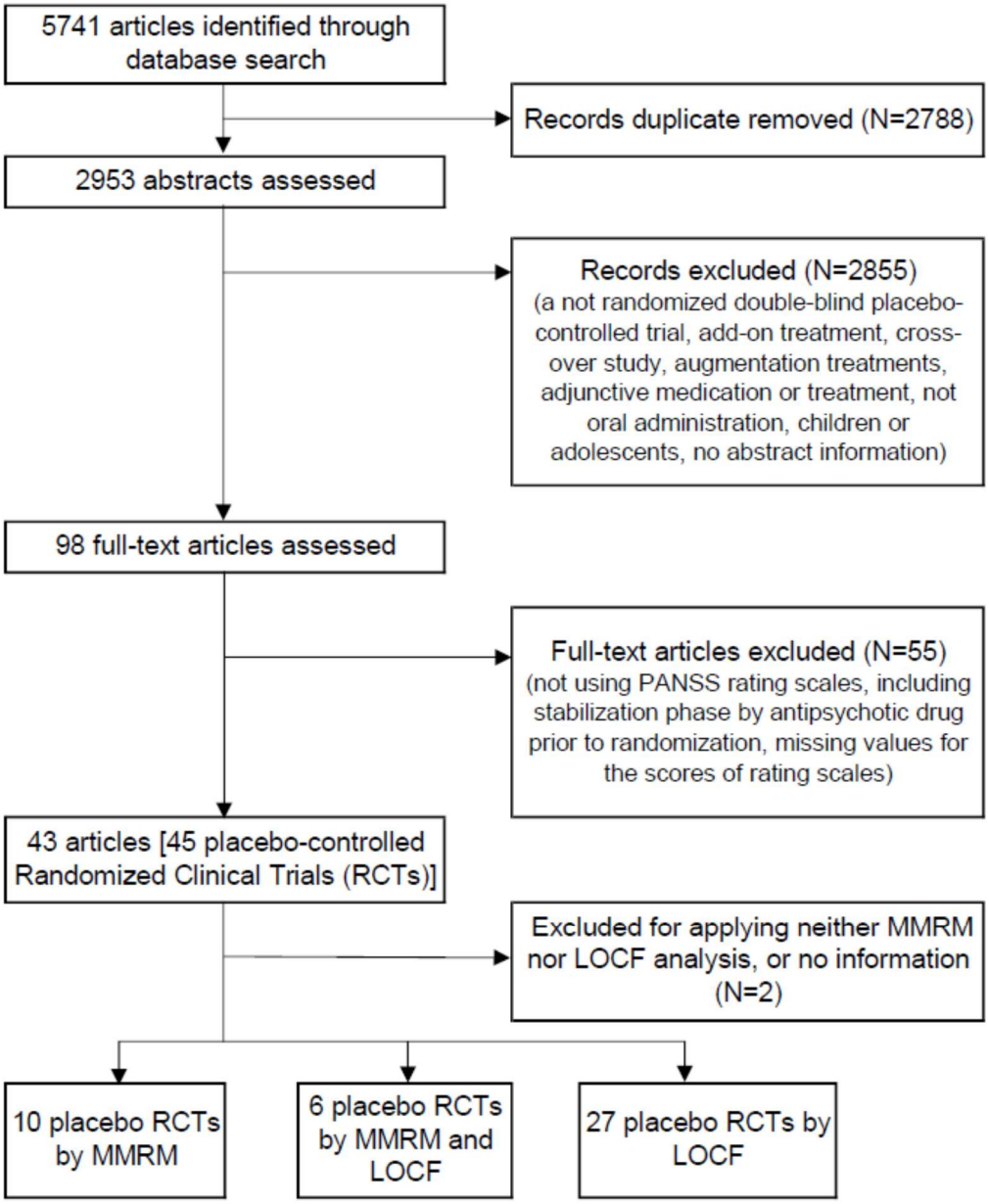

Figure 1. Article review and selection of studies

PANSS, Positive and Negative Syndrome Scale; LOCF, Last Observation Carried Forward; MMRM, Mixed-effect Models for Repeated Measures.

Table 1. Characteristics of identified placebo-controlled RCTs

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Study duration (week)	Mean PANSS total score at baseline	Mean change of PANSS total score from baseline	SE	Method of handling of Missing Data
1993	Guy Chouinard [34]	Risperidone	135	22	8	93.7	4.6	3.77	LOCF
1994	Stephen R. Marder [35]	Risperidone	378	64	8	92.2	3.3	2.78	LOCF
1996	Charles M. Beasley Jr [36]	Olanzapine	152	50	6	95.6	2.8	2.94	LOCF
1996	Daniel P. van Kammen [37]	Sertindole	153	38	5.71	57.6	-5.8	3.66	LOCF
1999	David G. Daniel [38]	Ziprasidone	302	92	6	97.3	-5.4		LOCF
1999	Philippe Truffinet [39]	Fananserin	97	34	4	93.4	-6.9	3.33	LOCF
2002	John M. Kane [40]	Aripiprazole	414	106	4	100.2	-2.90	2.37	LOCF
2003	Teresa A. Pigott [41]	Aripiprazole	310	155	26	83.12	4.50		LOCF
2003	Steven G. Potkin [42]	Aripiprazole	404	103	4	95.7	-5.00	2.17	LOCF
2006	Steven G. Potkin [43]	Resperidone, Quetiapine	382	73	2	94.3	-20.20	2.00	LOCF
2007	Michael Davidson [44]	Paliperidone ER	618	123	6	93.90	-2.80	1.88	LOCF
2007	Rene S. Kahn [45]	QuetiapineXR	588	118	6	96.20	-18.80	2.50	LOCF
2007	John M. Kane [46]	Paliperidone ER	630	127	6	94.10	-4.10	2.06	LOCF

continued

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Study duration (week)	Mean PANSS total score at baseline	Mean change of PANSS total score from baseline	SE	Method of handling of Missing Data
2007	Stephen R. Marder [47]	Pliperidone ER	444	110	6	93.60	-8.00	2.05	LOCF
2007	Joseph P. McEvoy [48]	Aripiprazole	420	108	6	92.30	-2.33	2.36	LOCF
2007	Steven G. Potkin [49]	Asenapine	182	62	6	92.43	-4.64	2.53	LOCF[a]
							-8.50	3.41	MMRM
2008	Daniel E. Casey [50]	Bifeprunox	589	119	6	92.10	-5.30	1.49	LOCF
2008	Andrew J. Culter [51]	Iloperidone	593	149	4	90.30	-7.08	1.48	MMRM[a]
							-6.80		LOCF
2008	Steven G. Potkin [52]	Iloperidone	621	127	6	94.60	-4.10	2.14	LOCF
2008	Steven G. Potkin [52]	Iloperidone	616	156	6	94.10	-3.50		LOCF
2008	Steven G. Potkin [52]	Iloperidone	706	160	6	94.90	-7.60		LOCF
2009	Carala M. Canuso [53]	Paliperidone ER	399	80	2	103.80	-15.00	2.20	LOCF
2009	Mitsutaka Nakamura [54]	Lurasidone	180	90	6	96.00	-5.50	2.20	LOCF
2010	Andrew J. Culter [55]	QuetiapineXR	565	117	6	90.80	-12.10	1.90	LOCF
2010	Jone M.Kane [56]	Asenepine	458	123	6	89.00	-10.70	1.57	LOCF[a]
							-14.60	1.61	MMRM

continued

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Study duration (week)	Mean PANSS total score at baseline	Mean change of PANSS total score from baseline	SE	Method of handling of Missing Data
2011	Bruce J. Kinon [57]	LY2140023	669	122	4	97.60	-14.60	2.20	MMRM
2011	Herbert Y. Meltzer [58]	Lurasidone	478	116	6	95.80	-16.00	2.10	MMRM[a]
							-15.20	1.70	LOCF
2011	Laura Redden [59]	ABT-925	156	48	6	87.10	-6.70	2.54	
2012	Mark E. Schmid [60]	JNJ37822681	498	101	6	90.20	-6.40	2.04	LOCF
2013	Michael F. Egan [61]	MK8998	216	83	4	97.4	-12.70	2.30	
2013	Antony Loebel [62]	Lurasidone	488	122	6	96.6	-10.30	1.80	MMRM
2013	Henry A. Nasrallah [14]	Lurasidone	500	129	6	96.8	-17.00	1.80	MMRM
2013	Masaaki Ogasa [63]	Lurasidone	149	50	6	93.3	-6.20	2.74	LOCF
2014	D. Bugarski-Kirola [64]	Bitopertin	301	80	4	65.2	-11.90	1.90	MMRM
2014	AnnCatherine M Downing [65]	LY2140023	1009	295	6	84.3	-7.90		MMRM
2014	Suresh Durgam [66]	Cariprazine	732	151	6	97.3	-11.84	1.54	LOCF[a]
							-13.30	1.80	MMRM
2014	Joan H.Q. Shen [67]	Vabicaserine	314	77	6	94.72	-2.70	2.44	LOCF

continued

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Study duration (week)	Mean PANSS total score at baseline	Mean change of PANSS total score from baseline	SE	Method of handling of Missing Data
2015	Christoph U. Correll [68]	Brexpiprazole	636	184	6	95.9	-12.01	1.60	MMRM
2015	Suresh Durgam [69]	Cariprazine	617	153	6	96.5	-14.30	1.50	MMRM
2015	Jone M.Kane [70]	Brexpiprazole	674	184	6	94.8	-13.53	1.52	MMRM
2015	John M. Kane [71]	Cariprazine	446	147	6	96.6	-16.00	1.60	MMRM
2015	Steven G. Potkin [15]	Lurasidone	353	72	6	96.5	-12.30	2.30	LOCF
2016	Toshihiko Kinoshita [72]	Asenapine	530	174	6	94.51	-0.95	1.53	LOCF
2016	Ronald Landbloom [73]	Asenapine	357	101	6	93.4	-16.20	1.71	MMRM
2016	Jeffrey A. Lieberman [74]	ITI-007	335	85	4	86.3	-7.40	1.68	MMRM[a]
							-6.30	1.60	LOCF

PANSS, Positive and Negative Syndrome Scale; LOCF, Last Observation Carried Forward; MMRM, Mixed-effect Models for Repeated Measures; RCTs, .Randomized Clinical Trials

[a] Primary analysis

2.3.2 Difference in the mean change of PANSS total score by MMRM versus LOCF in the placebo arm

A significant difference was identified in the mean change of PANSS score in the

placebo arm between MMRM and LOCF for the six studies for which both methods were applied (supplementary material A1).

2.3.3 Correlation between publication year and mean change of PANSS total score

There was no correlation between publication year from 2007 to 2016 and the mean change of PANSS total score in the placebo arm in MMRM-based data. The mean change of PANSS total score in the placebo arm in LOCF-based data did not strongly correlate with publication year from 1993 to 2016 (Figure 2).

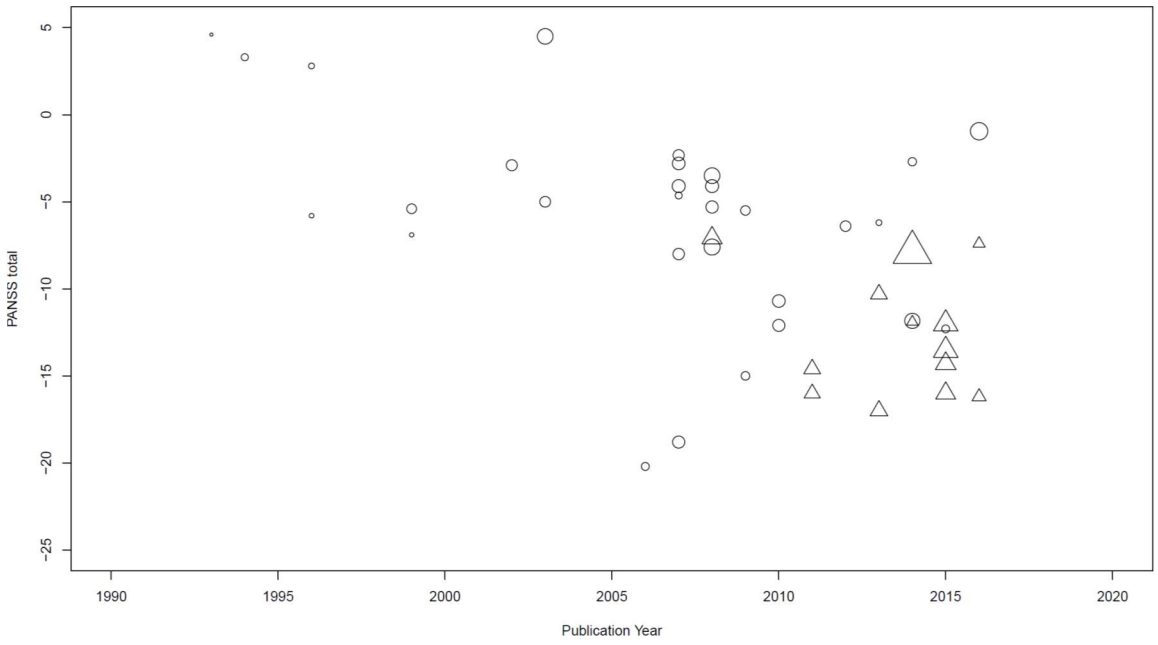

Figure 2. Relationship between publication year and the mean change of PANSS total score in the placebo arm

The sample size weighted correlation between the publication year and the mean change of PANSS total score in either LOCF-based data [○LOCF (weighted correlation r=-0.332)] or MMRM-based data [△MMRM (r=-0226)].

PANSS, Positive and Negative Syndrome Scale; LOCF, Last Observation Carried Forward; MMRM, Mixed-effect Models for Repeated Measures.

2.3.4 Univariate meta-regression analysis

When using the data to which MMRM was applied, univariate meta-regression analysis identified associations of the mean change of PANSS score with study duration, number of countries, number of study sites, enrollment speed, rater training, and treatment setting. When using the data to which LOCF was applied, the factors associated with the mean change of PANSS total score were diagnosis, study duration, placebo lead-in, and active comparator (Table 2).

2.3.5 Multivariate meta-regression analysis

In the multivariate meta-regression analysis of MMRM-based data, number of countries and treatment setting were significantly associated with the mean change of PANSS total score. In the multivariate meta-regression analysis of LOCF-based data, study duration was significantly associated with the mean change of PANSS total score (Table 2).

Table 2. Findings by meta-regression analyses in placebo-controlled RCTs by MMRM and LOCF

		Univariate meta-regression (MMRM)			Univariate meta-regression (LOCF)		
	Variable	Estimate	SE	p-value	Estimate	SE	p-value
Patient factors	Diagnosis				-9.304	3.107	0.003
	Severity	-0.127	0.104	0.225	-0.101	0.164	0.539
	Age	0.747	0.480	0.120	0.707	0.483	0.144
	% Male	0.149	0.094	0.111	0.104	0.112	0.352
Investigator factor	Rater training	-4.321	2.032	0.033	-2.384	2.279	0.295
Study design factors	Study duration	-2.130	0.740	0.004	2.267	0.757	0.003
	Placebo lead-in	-1.039	1.878	0.580	5.618	2.057	0.006
	Number of treatment arms	-1.241	1.205	0.303	0.774	1.123	0.491
	Placebo randomization rate	-0.014	0.236	0.953	0.160	0.162	0.324
	Regimen	2.466	1.658	0.137	-1.191	2.309	0.606
	Active comparator	-2.324	1.818	0.201	4.407	2.573	0.087
	Treatment setting	-3.463	1.425	0.015	-1.329	2.737	0.627
Operational factors	Number of study sites	-0.096	0.048	0.047	-0.023	0.049	0.640
	Number of countries	-0.653	0.297	0.028	-0.328	0.339	0.333
	Study period	-0.042	0.152	0.781	0.126	0.144	0.381
	Enrollment Speed	5.106	1.674	0.002	-0.782	3.293	0.812
		Multivariate meta-regression (MMRM)			Multivariate meta-regression (LOCF)		
	Variable	Estimate	SE	p-value	Estimate	SE	p-value
Patient factors	Diagnosis				-4.490	3.297	0.173
Investigator factor	Rater training	-3.607	2.990	0.228			
Study design factors	Study duration	0.866	1.231	0.482	1.567	0.747	0.036
	Placebo lead-in				2.994	2.119	0.158
	Active comparator				1.914	2.384	0.422
	Treatment setting	-4.217	1.971	0.032			
Operational factors	Number of study sites	0.149	0.092	0.106			
	Number of countries	-0.864	0.399	0.030			
	Enrollment speed	3.876	2.943	0.188			

LOCF, Last Observation Carried Forward; MMRM, Mixed-effect Models for Repeated Measures; RCTs, Randomized Clinical Trials.

2.4 Discussion

2.4.1 Placebo response and publication year

There was no correlation between publication year and the mean change of PANSS total score in the placebo arm in MMRM-based data. Placebo response in clinical trials of recent years was shown not to have increased over time. The result was inconsistent with that of the former reports that the placebo response in antipsychotic drug trials have increased over time [10-13]. It was considered that the main cause was due to the difference in the selection criteria for our analysis. We did not include the placebo RCTs before 1993 years which were contained in the previous analyses since the targeted placebo RCTs for our analysis had consistency in the primary endpoint or method of handling of missing data considering the changes of the RCTs characteristics. In addition, the possible cause might be due to the difference in the analysis method for confirming the correlation.

2.4.2 Difference in the mean change of PANSS total score between MMRM and LOCF

In 2010, the US National Research Council (NRC) of the National Academies of Science issued a report regarding the handling of missing data in clinical trials [25]. In the same year, a guideline on Missing Data in Confirmatory Clinical Trials was issued by

the Committee for Medicinal Products for Human Use (CHMP) in EU [24]. Consequently, the methodology of missing data handling in placebo-controlled RCTs for antipsychotic drugs has been shifting from LOCF to MMRM. Difference of concepts and characterizations between LOCF and MMRM affects the mean change of PANSS total score analyzed as primary efficacy [31, 22, 23]. It was reported that differences exist between MMRM and LOCF_ANCOVA (Analysis of covariance using the last observation carried forward approach to impute missing values) by comparing the results of the two analyses across eight clinical trials of duloxetine [31]. When meta-analysis is performed based on the data which came from the analysis of different concept, the possibility of impact on the result should be considered and the result should be interpreted with such a point of view. The present study is the first analyses focusing on the difference of methodology for the handling of missing data in relation to the degree of placebo response and the factors affecting the placebo response in clinical trials for antipsychotic drugs. As MMRM is being applied as a mainstream methodology, further investigation for identifying factors influencing the placebo response of clinical trial data based on MMRM are needed.

2.4.3 Potential influencing factors on placebo response

The potential factors on placebo response in MMRM-based data were the number of

countries conducting the study and the treatment setting during the study, such that more countries being involved and more freedom from hospitalization were significantly associated with greater placebo improvement. We suggest that differences in the healthcare environment among countries and in standardized care for schizophrenia affect the evaluation of antipsychotic drugs. The impact of changing the treatment setting on psychiatric symptoms in clinical trials might vary, depending on the quality of the hospitalization and the healthcare system. Differences in the standardized treatment for schizophrenia among countries might relate to the differences of concomitant medications given prior to participation in clinical trials; these previous medications can affect the efficacy of subsequent antipsychotic drugs. Countries which participate in clinical trials should be selected taking into consideration their standard medical treatment.

In LOCF-based data, our result showed the same as the previous study that shorter study duration increased placebo response [11]. Agid et al. proposed to ensure minimum six weeks for study duration to control the degree of placebo response [11]. Meanwhile, recent placebo-controlled RCTs for antipsychotic drugs are designed within six weeks as shown in Table 1. In future, study duration in placebo-controlled RCTs for new antipsychotic drugs should be set considering the point of ethical concerns for the

targeted patients [5].

2.5 Limitation

2.5.1 Analyzed Data

Our data were limited in that the mean change of PANSS total score from baseline and its standard deviation (SD), standard error (SE) and 95% confidence interval (CI), and also the mean of PANSS total score at baseline were not always presented in relevant documents including the published articles, FDA medical and statistical reviews and ClinicalTrials.gov, especially in studies with negative results. Those were not able to be included in our meta-regression analyses.

2.5.2 Number of studies for meta-regression analyses

MMRM and LOCF data were intermixed in the selected 43 placebo-controlled RCTs for our analyses due to the recent change in the methodology for handling missing data. Because the preliminary analysis based on six studies in which both MMRM and LOCF data were presented showed a significant difference in the mean change of PANSS score in the placebo arm between the two methods, we decided to conduct further meta-regression analysis separately for MMRM and LOCF-based data, which resulted in analysis with limited sample size. With the increase of clinical trials adopting MMRM in

the future, further investigation of MMRM-based data is warranted.

3. Research 2

3.1 Background and Objectives

Placebo-controlled RCTs have been largely adopted in recent antipsychotics clinical trials, and high dropout rates in the placebo arm of those RCTs have been reported in previous studies [16-18]. The mean dropout rate in the placebo arm of placebo-controlled RCTs of second- and first-generation antipsychotics was 60.2% and 63.3%, respectively [17], suggesting that dropout rates in the placebo arm have been high regardless of the type of antipsychotics. Dropout owing to lack of efficacy has been shown to be significantly higher in the placebo arm than that in the active treatment arm [17]. The length of the study was identified as a predictor of subject dropout [16, 18] with consistent results among previous studies. On the other hand, subject dropout rates in the placebo arm of RCTs of atypical antipsychotics have not been evaluated after the recent changes of the type of antipsychotics and the scale of psychiatric symptom assessment. In this study, we aimed to identify the potential factors affecting subject dropout in RCTs of atypical antipsychotics using a consistent psychiatric symptom assessment scale, PANSS, by a meta-analysis.

3.2 Methods

3.2.1 Search Strategy

We searched Medline, Embase, Cochrane Central Register of Controlled Trials, and PsycINFO using the keywords “Schizophrenia” and “Placebo”, and the following search limits: “Randomized controlled trial”, “Human and Humans”, “Adulthood” and “Publication year up to October 2018” to identify placebo-controlled RCTs of atypical antipsychoticss assessed by PANSS total score as a psychiatric symptom assessment tool.

3.2.2 Selection Criteria

Clinical trials that were not randomized double-blind placebo-controlled trials or did not use PANSS total score were excluded. Other exclusion criteria included studies on typical antipsychotics, add-on treatments, augmentation treatments, or adjunctive medication, studies with cross-over design or non-oral administration, studies for children or adolescents, and studies with stabilization phase by antipsychotic drugs prior to randomization.

3.2.3 Data Extraction

Data or values were extracted from the selected articles. Additionally, we referred to the U.S. Food and Drug Administration (FDA) medical and statistical reviews and ClinicalTrials.gov. Values of subject dropout were defined as the total number of subjects

who discontinued the clinical trials in the placebo arms. The total number of subject dropouts and the number of dropouts owing to either lack of efficacy or adverse event (AE) were extracted from the selected articles. When the selected articles provided only dropout rates, the number of subject dropouts was calculated using the dropout rates and number of subjects randomized to the placebo arm to conduct sample size- weighted analyses. Besides the known potential factors affecting subject dropout highlighted in previous studies on antipsychotics [16-18], unprecedented potential factors were added and categorized into the following groups:

- Year factor: publication year;
- Patient factors: diagnosis, severity, mean age at baseline, and % males;
- Study design factors: study duration, placebo lead-in, number of treatment arms, placebo randomization ratio, regimen, active comparator setting, and treatment setting;
- Operational factors: number of study sites, number of countries, and number of randomized subjects per study site.

Diagnosis was categorized to either DSM-III-R or DSM-IV-(TR). Severity was defined as the mean PANSS total score at baseline. Study duration was defined as the treatment period for subjects in the study and categorized into either studies with < 6-week

treatment period or studies with ≥ 6-week treatment period. Placebo lead-in was categorized into either studies with single/double-blind placebo lead-in period or those without it. Regimen was categorized into studies with a fixed dose throughout the study period, those with a fixed titration to a fixed maintenance dose, or those with a fixed titration to a flexible maintenance dose. Active comparator setting was categorized into either studies with active comparators or those without it. Treatment setting was categorized into either studies requiring hospitalization for the entire duration or those allowing hospital discharge during the study period according to the investigator's judgment. Number of randomized subjects per site was calculated as the total number of randomized subjects divided by the number of study sites.

The quality of the included published papers was assessed using Jadad score [30]. Two authors (A.M. and M.K.) independently assessed the selected studies and extracted data. Any disagreements were resolved by discussion between the two authors or consensus with another author (M.N.), as needed.

3.2.4 Data Analyses

Univariate meta-regression analyses for the potential factors affecting subject dropout were performed using the random-effects model. A significant association was defined as $p < 0.1$ in the univariate analysis. For those factors identified by the univariate analysis,

multivariate meta-regression analyses were then performed. These meta-regression analyses were performed separately for the total dropout, dropout owing to lack of efficacy, and dropout owing to AEs.

The meta-analyses were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [33] using R software version 3.4.0 [32].

3.3 Results

3.3.1 Included Studies for the Analysis

We identified 5,990 articles through the database search. After removing duplicated 2,898 articles, we reviewed 3,092 abstracts and excluded 2,992 articles based on their study design and other reasons. Then, we assessed 100 full-text articles and identified 45 articles with 47 placebo-controlled RCTs of atypical antipsychotics using PANSS (Figure 3). The characteristics of the 47 identified placebo-controlled RCTs of atypical antipsychotics are shown in Table 3 [34-62, 14, 63-71, 15, 72-76].

The mean Jadad score for the included published trials was 4.3, and they were shown to have adequate methodological quality

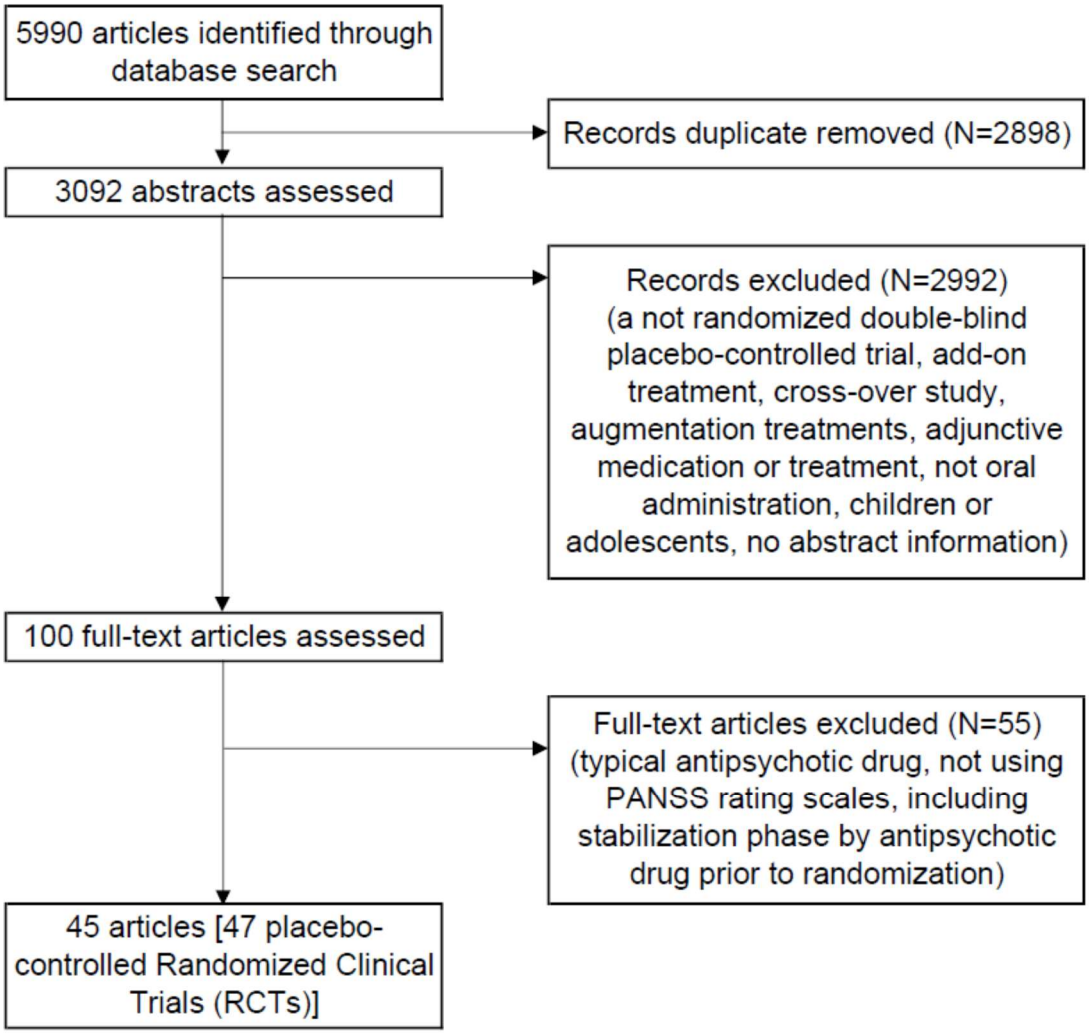

Figure 3. Article review and selection of studies

PANSS, Positive and Negative Syndrome Scale.

Table 3. Characteristics of identified placebo-controlled RCTs

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Number of Subjects discontinued from study (Total)	Number of Subjects discontinued from study (Lack of efficacy)	Number of Subjects discontinued from study (AE)	Study duration (week)	Mean PANSS total score at baseline
1993	Guy Chouinard [34]	Risperidone	135	22	16	10	1	8	93.7
1994	Stephen R. Marder [35]	Risperidone	378	64	44	40		8	92.2
1996	Charles M. Beasley Jr [36]	Olanzapine	152	50	40	37	0	6	95.6
1996	Daniel P. van Kammen [37]	Sertindole	153	38		13	2	5.71	57.6
1999	David G. Daniel [38]	Ziprasidone	302	92	9	3	3	6	97.3
1999	Philippe Truffinet [39]	Fananserin	97	34	47	32	1	4	93.4
2002	John M. Kane [40]	Aripiprazole	414	106	48	15	17	4	100.2
2003	Teresa A. Pigott [41]	Aripiprazole	310	155	52	18	18	26	83.12
2003	Steven G. Potkin [42]	Aripiprazole	404	103	110	76	13	4	95.7
2006	Steven G. Potkin [43]	Resperidone, Quetiapine	382	73	13			2	94.3
2007	Michael Davidson [44]	Paliperidone ER	618	123	73	39	6	6	93.9
2007	Rene S. Kahn [45]	QuetiapineXR	588	118	41	18	7	6	96.2

continued

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Number of Subjects discontinued from study (Total)	Number of Subjects discontinued from study (Lack of efficacy)	Number of Subjects discontinued from study (AE)	Study duration (week)	Mean PANSS total score at baseline
2007	John M. Kane [46]	Paliperidone ER	630	127	78	11	6	6	94.1
2007	Stephen R. Marder [47]	Pliperidone ER	444	110	33	17	3	6	93.6
2007	Joseph P. McEvoy [48]	Aripiprazole	420	108	76	54	5	6	92.3
2007	Steven G. Potkin [49]	Asenapine	182	62	69	51	9	6	92.43
2008	Daniel E. Casey [50]	Bifeprunox	589	119	60	48	28	6	92.1
2008	Andrew J. Culter [51]	Iloperidone	593	149	70	27	13	4	90.3
2008	Steven G. Potkin [52]	Iloperidone	621	127	88	44	8	6	94.6
2008	Steven G. Potkin [52]	Iloperidone	616	156	94	64	11	6	94.1
2008	Steven G. Potkin [52]	Iloperidone	706	160	74	46	6	6	94.9
2009	Carala M. Canuso [53]	Paliperidone ER	399	80	14	6	4	2	103.8
2009	Mitsutaka Nakamura [54]	Lurasidone	180	90	43	29	1	6	96
2010	Andrew J. Culter [55]	QuetiapineXR	565	117	53	31	4	6	90.8
2010	Jone M.Kane [56]	Asenepine	458	123	49	15	14	6	89
2011	Bruce J. Kinon [57]	LY2140023	669	122	23	15	4	4	97.6

continued

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Number of Subjects discontinued from study (Total)	Number of Subjects discontinued from study (Lack of efficacy)	Number of Subjects discontinued from study (AE)	Study duration (week)	Mean PANSS total score at baseline
2011	Herbert Y. Meltzer [58]	Lurasidone	478	116	49	33	4	6	95.8
2011	Laura Redden [59]	ABT-925	156	48	45	18	10	6	87.1
2012	Mark E. Schmid [60]	JNJ37822681	498	101	52	34	3	6	90.2
2013	Michael F. Egan [61]	MK8998	216	83	21	15	0	4	97.4
2013	Antony Loebel [62]	Lurasidone	488	122	48	28	5	6	96.6
2013	Henry A. Nasrallah [14]	Lurasidone	500	129	55	32	3	6	96.8
2013	Masaaki Ogasa [63]	Lurasidone	149	50	35	16	2	6	93.3
2014	D. Bugarski-Kirola [64]	Bitopertin	301	80	72	33	22	4	65.2
2014	AnnCatherine M Downing [65]	LY2140023	1009	295	49	13	11	6	84.3
2014	Suresh Durgam [66]	Cariprazine	732	151	22	9	2	6	97.3
2014	Joan H.Q. Shen [67]	Vabicaserine	314	77	75	18	32	6	94.72
2015	Christoph U. Correll [68]	Brexpiprazole	636	184	124	48	33	6	95.9
2015	Suresh Durgam [69]	Cariprazine	617	153	66	21	22	6	96.5

continued

Publication Year	Reference	Antipsychotics	Number of Randomized Subjects (total)	Number of Randomized Subjects to Placebo	Number of Subjects discontinued from study (Total)	Number of Subjects discontinued from study (Lack of efficacy)	Number of Subjects discontinued from study (AE)	Study duration (week)	Mean PANSS total score at baseline
2015	Jone M.Kane [70]	Brexpiprazole	674	184	36	13	4	6	94.8
2015	John M. Kane [71]	Cariprazine	446	147	58	20	17	6	96.6
2015	Steven G. Potkin [15]	Lurasidone	353	72	59	26	13	6	96.5
2016	Toshihiko Kinoshita [72]	Asenapine	530	174	40	21	10	6	94.51
2016	Ronald Landbloom [73]	Asenapine	357	101	94	27	43	6	93.4
2016	Jeffrey A. Lieberman [74]	ITI-007	335	85	19	8	0	4	86.3
2017	Marc Cantillon [75]	RP5063	234	39	10	8	0	4	89.8
2018	Jun Ishigooka [76]	Brexpiprazole	459	116	46	7	21	6	97.1

AE, Adverse Event; PANSS, Positive and Negative Syndrome Scale; RCTs, Randomized Clinical Trials.

3.3.2 Univariate Meta-regression Analysis

Univariate meta-regression analysis identified associations between subject dropout rates and publication year, diagnosis, age, study duration, placebo lead-in, and treatment

setting (Table 4). Using the data of dropout owing to lack of efficacy as a response variable, publication year, diagnosis, study duration, and number of study sites were associated with dropout rates owing to lack of efficacy (Table 5). Additionally, diagnosis, age, and number of study sites were associated with dropout rates owing to AEs (Table 6).

3.3.3 Multivariate Meta-regression Analysis

In the multivariate meta-regression analysis for total number of subject dropout-based data, publication year, age, and study duration were significantly associated with the dropout rates (Table 4). Publication year and study duration were also identified as factors affecting dropout rates owing to lack of efficacy in the multivariate meta-regression analysis (Table 5). In the analysis of dropout rates owing to AEs, the number of study sites was significantly associated with dropout rates (Table 6).

Table 4. Findings in subject dropout by meta-regression analyses in placebo-controlled RCTs

		Univariate meta-regression			Multivariate meta-regression		
	Variable	Estimate	SE	p-value	Estimate	SE	p-value
Year factor	Publication Year	-0.012	0.004	0.001	-0.012	0.004	0.002
Patient factors	Diagnosis	-0.224	0.080	0.005	-0.014	0.090	0.880
	Severity	0.000	0.004	0.959			
	Age	0.019	0.010	0.058	0.016	0.008	0.044
	% Male	0.002	0.002	0.283			
Study design factors	Study duration	0.213	0.045	0.000	0.214	0.056	0.000
	Placebo lead-in	0.078	0.045	0.086	0.021	0.034	0.533
	Number of treatment arms	0.020	0.024	0.403			
	Placebo randomization rate	0.002	0.003	0.425			
	Regimen (1)	-0.074	0.047	0.116			
	Regimen (2)	0.021	0.113	0.851			
	Active comparator	0.071	0.051	0.158			
	Treatment setting	0.110	0.047	0.018	-0.028	0.049	0.565
Operational factors	Number of countries	-0.009	0.007	0.221			
	Number of study sites	0.000	0.001	0.886			
	Number of randomized subjects per site	-0.003	0.003	0.419			

RCTs, randomized clinical trials.

Table 5. Findings in subject dropout (lack of efficacy) by meta-regression analyses in placebo-controlled RCTs

		Univariate meta-regression			Multivariate meta-regression		
	Variable	Estimate	SE	p-value	Estimate	SE	p-value
Year factor	Publication Year	-0.014	0.003	0.000	-0.010	0.004	0.005
Patient factors	Diagnosis	-0.287	0.060	0.000	-0.112	0.077	0.145
	Severity	-0.002	0.003	0.564			
	Age	-0.011	0.009	0.255			
	% Male	0.001	0.002	0.774			
Study design factors	Study duration	0.089	0.047	0.059	0.111	0.038	0.003
	Placebo lead-in	0.060	0.041	0.141			
	Number of treatment arms	0.011	0.022	0.605			
	Placebo randomization rate	0.002	0.003	0.525			
	Regimen (1)	-0.029	0.043	0.494			
	Regimen (2)	0.090	0.103	0.385			
	Active comparator	0.030	0.045	0.515			
	Treatment setting	0.070	0.044	0.112			
Operational factors	Number of countries	0.001	0.006	0.822			
	Number of study sites	-0.001	0.001	0.068	-0.001	0.001	0.437
	Number of randomized subjects per site	0.000	0.003	0.997			

RCTs, randomized clinical trials.

Table 6. Findings in subject dropout (AE) by meta-regression analyses in placebo-controlled RCTs

		Univariate meta-regression			Multivariate meta-regression		
	Variable	Estimate	SE	p-value	Estimate	SE	p-value
Year factor	Publication Year	0.002	0.001	0.205			
Patient factors	Diagnosis	0.052	0.029	0.075	0.018	0.030	0.554
	Severity	0.001	0.001	0.432			
	Age	0.010	0.004	0.005	0.007	0.004	0.067
	% Male	0.000	0.001	0.622			
Study design factors	Study duration	0.013	0.020	0.520			
	Placebo lead-in	-0.003	0.017	0.844			
	Number of treatment arms	-0.004	0.009	0.689			
	Placebo randomization rate	0.000	0.001	0.892			
	Regimen (1)	0.001	0.018	0.968			
	Regimen (2)	-0.020	0.041	0.616			
	Active comparator	-0.001	0.018	0.974			
	Treatment setting	-0.007	0.020	0.709			
Operational factors	Number of countries	-0.002	0.003	0.383			
	Number of study sites	0.001	0.000	0.000	0.001	0.000	0.007
	Number of randomized subjects per site	-0.001	0.001	0.357			

AE, Adverse Event; RCTs, randomized clinical trials.

3.4 Discussion

Our meta-regression analyses were performed using data of total subject dropout, dropout owing to lack of efficacy, and dropout owing to AEs. In particular, we focused on the factors affecting subject dropout owing to lack of efficacy since subject dropout most frequently occurs in the placebo arm [17]. Total subject dropout rates and dropout rates owing to lack of efficacy were strongly associated with long study duration. These results were consistent with the findings of previous studies on dropout rates in RCTs of antipsychotics [16, 18]. In our analyses, study duration, defined as the treatment period for the randomized subjects, was categorized into either studies with < 6 weeks or those with ≥ 6 weeks. Studies with a duration ≥ 6 weeks were significantly associated with a high dropout rate, compared to those with a duration < 6 weeks. We suggested that < 6-week study duration should be adopted in future RCTs of new antipsychotics taking into account the following points: appropriate evaluation of the efficacy of new antipsychotics, the mechanism of new antipsychotics, and ethical concerns related to the target subjects.

Our meta-regression analyses also showed significant association between the publication year and subject dropout rates for both total dropout and dropout owing to lack of efficacy, suggesting that the frequency of subject dropout has decreased in recent placebo-controlled RCTs of atypical antipsychotics. This might implicate that recent

study designs, such as limits of permitted concomitant medications during the study and inclusion and exclusion criteria for previous medications prior to enrollment, might contribute to the decrease in subject dropout rates in recent RCTs.

In the present study, we found that older age was also associated with subject dropout for total dropout and dropout owing to AEs. This might be attributed to the longer period of illness in older subjects, implying that they might have changed their antipsychotic treatment several times and might not be satisfied with their antipsychotic treatment. Subject satisfaction with antipsychotic treatment could be related to remaining in clinical trials for a longer period of time [77, 78]. Relations between medication satisfaction and older age, period of illness, and history of medications need to be assessed in further analyses.

3.5 Limitation

Our data for the analysis were limited in that the information of total dropout rates and dropout in each reason, and also the data of potential factors affecting subjects' dropout were not always presented in the relevant documents including the published articles, FDA medical and statistical reviews and ClinicalTrials.gov, especially for studies published earlier. Those were not able to be included in our meta-regression analyses. Our

study also has a limitation related to analyses of dropout owing to various reasons. The criteria of categorizing the reason for dropout might vary according to the clinical trial protocol. In five RCTs [40, 68, 70, 72, 76], the number of dropouts owing to AEs was higher than that owing to lack of efficacy although a previous study reported that the main reason for dropout in the placebo arms was the lack of efficacy [17]. This discrepancy might be explained that in those studies, dropouts owing to deterioration of schizophrenia symptoms were not counted as dropouts owing to lack of efficacy but as dropouts owing to AEs. Clarifying the trial objectives, taking into consideration intercurrent events, which lead to withdrawal from clinical trials or dropout, and handling of the missing data owing to dropouts should be deeply considered in future clinical trials.

4. Overall Discussion and Conclusion

In our research, placebo response in RCTs for antipsychotics published between 1993 and 2016 was shown not to have increased over time, and subject dropout rates in RCTs published between 1993 and 2018 have decreased. These were new findings which were different from the previous reports. The main cause was considered to be the differences in the selection criteria for studies between the researches. Placebo-controlled RCTs before 1993 contained in the previous research were not included in our study because

we conducted the present study considering the recent changes in the diagnostic criteria, primary variables for the assessment of drug efficacy, and the handling of missing data in RCTs for antipsychotics. When we refer to meta-analysis based on data from clinical studies in which different methods such as the handling of missing data, MMRM and LOCF, or the assessments scale, BPRS and PANSS, were applied, we should carefully consider the aforementioned changes and their impact on the results of the analysis.

The potential factors influencing the placebo response in MMRM-based data were the number of countries conducting the study and the treatment setting during the study, which means that more participating countries in clinical studies and patients' freedom from hospitalization would result in greater placebo improvement. Also, it was shown that older age of patients and longer study duration would lead to high dropout rates.

In designing placebo-controlled RCTs for antipsychotics, in order to adequately control the degree of placebo response, the number of countries participating in the study and the duration/condition of patient hospitalization during the study should be considered. Also, study design with as short a duration as possible, with due consideration of the mode of action of the new antipsychotics, would decrease subjects' dropout in future placebo-controlled RCTs.

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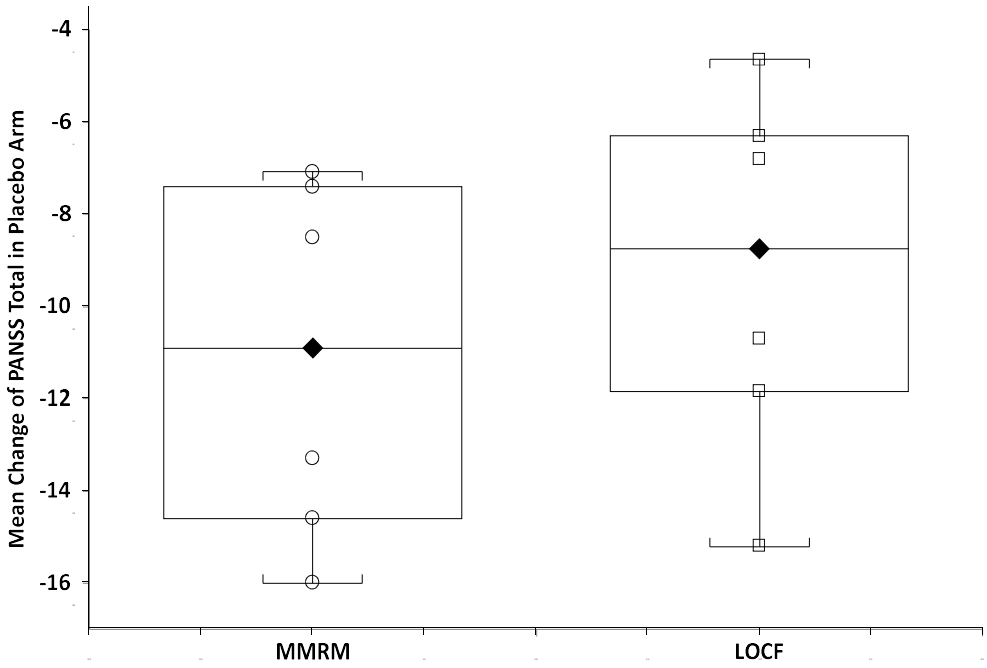

Appendix 1. Difference in Mean Change of PANSS total score by MMRM versus LOCF

Paired t-test for six studies that provided both values of mean change of PANSS total score based on MMRM and LOCF (two sided p-value: 0.032).