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ORIGINAL RESEARCH

Iminodibenzyl class antipsychotics for schizophrenia: a systematic review and meta-analysis of carpipramine, clocapramine, and mosapramine

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Background: We conducted a meta-analysis of the iminodibenzyl antipsychotics carpipramine, clocapramine, and mosapramine, which are classified as second-generation antipsychotics (SGAs) for schizophrenia treatment.

Methods: We searched data that had been published in PubMed, the Cochrane Library databases, PsycINFO, CiNii, and the Japan Medical Abstracts Society up to August 29, 2014. Randomized controlled trials that compared iminodibenzyl antipsychotics with other antipsychotics in patients with schizophrenia were included. Odds ratios and standardized mean differences were evaluated.

Results: We included four randomized controlled trials on carpipramine (number of patients [n]=290), six on clocapramine (n=1,048), and five on mosapramine (n=986) in the meta-analysis. There were no significant differences in the response rates or in the discontinuation rates either between carpipramine and the other pooled antipsychotics or between clocapramine and the other pooled antipsychotics. On the Positive and Negative Syndrome Scale, mosapramine's positive subscale scores were superior to those of the other pooled antipsychotics (standard mean of difference =–0.22); however, on that same scale, there were no significant differences in total scores, negative scores, general subscale scores, response rates, or the discontinuation rates between mosapramine and the other pooled antipsychotics. Furthermore, the incidences of extrapyramidal symptoms and of hyperprolactinemia were significantly greater with mosapramine than with the other pooled antipsychotics.

Conclusion: The pharmacological profiles of carpipramine and clocapramine, which are classified as SGAs, were similar to those of first-generation antipsychotics because there were no significant differences in efficacy and safety outcomes. However, mosapramine was associated with a greater risk of extrapyramidal symptoms and hyperprolactinemia than the other SGAs were, although it may be beneficial for the improvement of positive symptoms.

Keywords: carpipramine, clocapramine, mosapramine, schizophrenia, meta-analysis

Introduction

A meta-analysis of carpipramine, clocapramine, and mosapramine, medications that have been classified in the iminodibenzyl class of antipsychotics[1,2] for schizophrenia treatment, has not been reported. A meta-analysis is considered to present a higher level of evidence than individual trials.[3] Employing a meta-analysis can increase the statistical power for deducing treatment effects by correspondingly narrowing the confidence intervals. This, in turn, increases the precision of the effect size. A systematic review

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and meta-analysis can overcome the limitations of small studies and cover broader outcome measures.[3]

Iminodibenzyl class antipsychotics are structurally related to both tricyclic antidepressants such as imipramine, and butyrophenones such as haloperidol.[4] Although carpipramine is available in both Japan and France, clocapramine and mosapramine are only available in Japan. However, iminodibenzyl antipsychotics are not available in the United States. According to an in vivo study that evaluated the binding profile of clocapramine to striatal dopamine D_2 receptors and frontal serotonin (5-HT_2) receptors in a rat brain, clocapramine and mosapramine exhibited potency in occupying the D_2 receptors and 5-HT_2 receptors.[1] On the basis of this evidence, clocapramine and mosapramine are classified as second-generation antipsychotics (SGAs). However, the D_2 receptor/5-HT_2 receptor occupancy ratios of clocapramine (3) and of mosapramine (7.4) were similar to those of chlorpromazine (4.6) and of zotepin (4.3), but lower than the ratio of clozapine (49).[1] Mosapramine was selected as a comparator in the three clinical Phase III trials of aripiprazole, quetiapine, and perospirone for the treatment of schizophrenia in Japan.[5–7] Carpipramine is also classified as an SGA because it was reported to exhibit a D_2 receptor/5-HT_2 receptor antagonist effect.[1] However, the D_2 receptor/5-HT_2 receptor occupancy ratio is perhaps not relevant to the classification of SGA. This systematic review and meta-analysis aimed to elucidate the clinical and pharmacological characteristics of carpipramine, clocapramine, and mosapramine, such as efficacy, effectiveness, safety, and tolerability, in patients with schizophrenia.

Methods

This meta-analysis was performed according to the guidelines of Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) 2009 (Supplementary material 1).[8] We performed a systematic literature review according to the Patient Intervention Comparator Outcome strategy (patients: schizophrenia; intervention: carpipramine, clocapramine, or mosapramine; comparator: other antipsychotics; and outcome: efficacy and safety).

Inclusion criteria, search strategies, and data extraction

Eligibility for the study was based on the following inclusion criteria: 1) randomized controlled trials (RCTs) comparing the iminodibenzyl class of antipsychotics (carpipramine, clocapramine, and mosapramine) with other antipsychotics; 2) diagnosis of schizophrenia spectrum disorders, including schizophrenia and schizoaffective disorder; and 3) study duration of ≥8 weeks. To identify the relevant studies, we searched PubMed, the Cochrane Library databases, PsycINFO, CiNii, and Japan Medical Abstracts Society citations that had been published up to August 29, 2014 (in English or in Japanese) by using the following keywords: ("carpipramine" OR "clocapramine" OR "mosapramine") AND "schizophrenia". In addition, we used the drug package insert in each antipsychotic (carpipramine, http://di.mt-pharma.co.jp/file/if/f_def.pdf; clocapramine, http://di.mt-pharma.co.jp/file/if/f_clo.pdf; and mosapramine, http://di.mt-pharma.co.jp/file/dc/cre.pdf). Moreover, we consulted with Mitsubishi Tanabe Pharma, which manufactures and sells these three antipsychotic drugs, in regard to the clinical Phase III trials for these drugs. Three authors (Taro Kishi, Shinji Matsunaga, and Yuki Matsuda) scrutinized the inclusion and exclusion criteria of the identified studies. The search was further limited to RCTs. The references of the included articles and review articles in this area were searched for citations of additional relevant published and unpublished research. When data required for the meta-analysis were missing, either the first or the corresponding author was contacted for additional information. Three authors (Taro Kishi, Shinji Matsunaga, and Yuki Matsuda) independently extracted, checked, and entered this data into Cochrane Collaboration Review Manager Version 5.2 for Windows (http://tech.cochrane.org/Revman, Cochrane Collaboration, Oxford, UK).

Outcomes and data synthesis

We based the analyses on intention-to-treat or modified intention-to-treat data (such as at least one dose or one follow-up assessment). In order to perform a meta-analysis, we required at least two studies with the same outcome measure. With regard to the carpipramine and clocapramine studies, the response rates were set as the primary outcomes. We pooled the response rates that were defined as very much or much improved according to a global scale. The discontinuation rates due to all causes, inefficacy, and side effects were set as the secondary outcomes. For the mosapramine studies, the change in the Positive and Negative Syndrome Scale (PANSS)[9] scores for total, positive, negative, and general psychopathology symptoms and response rates were set as the primary outcomes, and discontinuation rates due to all causes, inefficacy, side effects, death, and death by suicide were set as the secondary outcomes. We pooled the response rates as defined by the studies included in the meta-analysis (the Final Global Improvement Rating, the Global

Comprehensive Judgment, the Global Improved Rating and the Global Judgment). Meta-analyses of individual side effects were also included. For the extrapyramidal side-effect rating scales of mosapramine studies, one of the three studies included in the meta-analysis used the change in the Drug-Induced Extrapyramidal Symptom Scale[10] total scores; the scores from that study were the worst scores in our study. One study used the last observational scores of the Drug-Induced Extrapyramidal Symptom Scale, while another used the change in the Keio Extrapyramidal Symptoms Rating Scale[11] scores during the study.

Statistical analysis

The meta-analysis was performed by using Review Manager software. To combine studies, the random effects model by DerSimonian and Laird,[12] which is the most conservative, was used in all cases because the populations with these diseases tended to be heterogeneous and could generate effect size differences. For continuous data, standardized mean differences (SMDs) that combined the effect size data (Hedges' g) were used. For dichotomous data, the odds ratio (OR) for each set of data was estimated along with the 95% confidence interval (CI). In this study, if the random effects model showed significant differences among groups, the number needed to harm (NNH) was calculated. Then, the NNH values were derived from the risk differences (RD) by using the following formula:

$$NNH = 1/RD$$

with the 95% CIs of NNH being the inverse of the upper and lower limits of the 95% CI of the RD. We explored study heterogeneity by using the I^2 statistics and considering values of ≥50% to reflect considerable heterogeneity.[13] In cases of I^2 values that were ≥50% for the primary outcomes, we planned to conduct sensitivity analyses to determine the reasons for the heterogeneity. However, we did not detect significant heterogeneities in any of the primary outcomes in the meta-analyses of carpipramine, clocapramine, and mosapramine.

Results

With regard to the results of the literature search, we showed a PRISMA flow chart for each antipsychotic drug (Supplementary material 2). We included four RCTs[14–17] in the meta-analysis for carpipramine, six[18–23] for clocapramine, and five[5–7,18,24] for mosapramine (Table 1). Other than the Yamagami et al study,[20] all of the studies had relatively high methodological quality according to the Cochrane Risk of Bias Criteria because these studies were double-blind RCTs and had mentioned the required details of the study design. The Yamagami et al study,[20] however, was a single-blind RCT (Supplementary material 3). The characteristics of the included studies are shown in Table 1.

The results of meta-analysis of carpipramine RCTs

All comparators of RCTs that were included in the meta-analysis of carpipramine were first-generation antipsychotics (FGAs) (clofluperol, oxypertine, penfluridol, and pimozide). In the comparisons of carpipramine with the other pooled or individual antipsychotics, there were no significant differences between the treatment groups in response rates, discontinuation rates, or individual side effects other than fatigue (Table 2; Supplementary material 4.1). Carpipramine was associated with less fatigue than oxypertine (OR=0.11; NNH=5; Table 2; Supplementary material 4.1).

The results of meta-analysis of clocapramine RCTs

The comparators in the meta-analysis of clocapramine RCTs were FGAs (bromperidol, haloperidol, perphenazine, and sulpride) and SGAs (mosapramine and risperidone). Clocapramine did not differ from other pooled antipsychotics in response rates or discontinuation rates, although there were differences in the incidences of headaches and decreased appetite (Table 3; Supplementary material 4.2). When we performed a subgroup analysis of response rates stratified according to FGA and SGA comparators, clocapramine was found to be comparable to the pooled FGAs (OR=0.93) and marginally inferior to the pooled SGAs (OR=1.51; P=0.06). In comparisons between clocapramine and other pooled antipsychotics, clocapramine was associated with lower incidences of headaches and decreased appetite (headache [OR=0.47; NNH, not significant]; decreased appetite [OR=0.57; NNH, not significant]; Table 3; Supplementary material 4.2). In individual antipsychotic comparisons, clocapramine was associated with a lower incidence of tremors than mosapramine (OR=0.34; NNH=7), with lower incidences of nausea and vomiting than perphenazine (OR=0.38; NNH=25), and with a lower incidence of decreased appetite than haloperidol (OR=0.35; NNH=7; Table 3; Supplementary material 4.2).

The results of meta-analysis of mosapramine RCTs

The comparators in the meta-analysis of mosapramine RCTs were an FGA (haloperidol) and several SGAs (aripiprazole,

Table 1 Study, patient, and treatment characteristics of the included randomized controlled trials

Study	Comparators	Total n	Patients (%)	Diagnosis	Duration	Age, mean ± SD (range)
CAR studies						
Ito et al[17], double-blinded, industry	CFP	90	Inpatients (100). Inclusion criteria: duration of illness ≥3 years; no obvious positive symptoms; and significant negative symptoms. Exclusion criteria: excitement and/or intellectual disability	NR	8 weeks (no washout phase)	CAR: 36.7±9.0; CFP: 36.7±–8.9
Tanimukai and Kaneko[16], double-blinded, industry	OXY	58	Inpatients (100). Inclusion criteria: excitement; positive symptoms; and/or negative symptoms	NR	10 weeks (including 2 weeks of PBO and washout phase)	CAR: 35.9±8.1; OXY: 37.0±0.8
Kondo et al[15], double-blinded, industry	PEN	86	Inpatients (100). Inclusion criteria: positive symptoms and/or negative symptoms. Exclusion criteria: excitement and/or hebephrenia	NR	8 weeks (including a 3–7-day washout phase)	CAR: 39.0; PEN: 37.7, (15–60)
Kudo et al[14], double-blinded, industry	PIM	56	Inpatients (100). Inclusion criteria: positive symptoms and/or negative symptoms	NR	8 weeks (preceded by a several-day washout)	(<60)
CCP studies						
Kudo et al[21], double-blinded, industry	BPD	169	Inpatients and outpatients. Exclusion criteria: exacerbation; stupor; and/or hebephrenia	NR	8 weeks (no washout phase)	CCP: 39.4; BPD: 38.9
Mukasa et al[22], double-blinded, industry	BPD	136	Inpatients (100). Inclusion criteria: positive symptoms and/or negative symptoms. Exclusion criteria: exacerbation; stupor; and/or hebephrenia	NR	8 weeks (no washout phase)	(20–60)
Kurihara et al[23], double-blinded, nonindustry	HAL, PPZ	286	Inpatients (100). Inclusion criteria: positive symptoms and negative symptoms. Exclusion criteria: exacerbation; stupor; and/or hebephrenia	NR	8 weeks (no washout phase)	(NR)
Kato et al[18], double-blinded, industry	MOS	205	Inpatients and outpatients Exclusion criteria: exacerbation; stupor; and/or hebephrenia	ICD-9	8 weeks (no washout phase)	(16–64)
Kudo et al[19], double-blinded, industry	RIS	200	Exclusion criteria: exacerbation; stupor; and/or hebephrenia	ICD-9 and DSM-III-R	8 weeks (no washout phase)	CCP: 41±14, RIS: 42±14, (19–65)
Yamagami et al[20], single-blinded, nonindustry	SUL	52	Exclusion criteria: stupor and/or hebephrenia	NR	8 weeks (no washout phase)	(18–59)
MOS studies						
031-95-003[5], double-blinded, industry	ARI	238	Schizophrenia	ICD-10	8 weeks	MOS: 45.2±12.7; ARI: 45.5±12.4 (16–65)

Male, %	Ethnicity (%)	AP	n	Dose (mg/day)	Concomitant drugs (%)	Efficacy outcomes
CAR: 66.7; CFP: 62.2	Japanese (100)	CAR	45	Mean dose: NR; max dose: 300; flexible	Anti-C (NR), SP (NR)	Response rate (GIR): CAR=CFP
		CFP	45	Mean dose: NR; max dose: 6; flexible	Anti-C (NR), SP (NR)	
CAR: 34.4; OXY: 34.4	Japanese (100)	CAR	29	Mean dose: NR; max dose: 300; flexible	NR	Response rate (GIR): CAR=OXY
		OXY	29	Mean dose: NR; max dose: 240; flexible	NR	
CAR: 77.3; PEN: 66.7	Japanese (100)	CAR	42	Mean dose: NR; max dose: 200; fixed	PMZ (100)	Response rate (GCJ): CAR<PEN
		PEN	44	Mean dose: NR; max dose: 80; fixed	PMZ (100)	
CAR: 50.0; PIM: 50.0	Japanese (100)	CAR	28	Mean dose: NR; range: 75–200; flexible	Anti-C (NR), SP (NR)	Response rate (GJ): CAR=PIM
		PIM	28	Mean dose: NR; range: 3–8; flexible	Anti-C (NR), SP (NR)	
CCP: 50.6; BPD: 58.0	Japanese (100)	CCP	81	Mean dose: 138.8±6.0; range: 25–225; flexible	AP (2.5), AX (4.9), anti-C (51.9), SP (46.9)	Response rate (FGIR): CCP=BPD
		BPD	88	Mean dose: 9.8±0.42; range: 2–18; flexible	AP (3.4), AX (10.2), anti-C (56.8), SP (44.3)	
CCP: 51.4; BPD: 52.3	Japanese (100)	CCP	70	Mean dose: NR; range: 25–225; flexible	AP (NR), AX (NR), anti-C (NR), SP (NR)	Response rate (FGIR): CCP=BPD
		BPD	66	Mean dose: NR; range: 2–18; flexible	AP (NR), AX (NR), anti-C (NR), SP (NR)	
CCP: 56.7, HAL: 57.4, PPZ: 53.7	Japanese (100)	CCP	97	Mean max dose: 173.2; range: 75–225; flexible	AP (0.0), AX (1.0), anti-C (60.8), SP (46.4)	Response rate (FGIR): CCP= HAL=PPZ
		HAL	94	Mean max dose: 7.2; range: 1–9; flexible	AP (3.2), AX (4.3), anti-C (61.7), SP (50.0)	
		PPZ	95	Mean max dose: 21.6; range: 3–27; flexible	AP (4.2), AX (1.1), anti-C (53.7), SP (49.5)	
CCP: 61.8; MOS: 57.3	Japanese (100)	CCP	102	Max dose: 200; flexible	AP (1.0), AX (2.0), anti-C (19.6), SP (10.8)	Response rate (FGIR): CCP=MOS
		MOS	103	Max dose: 120; flexible	AP (4.9), AX (3.9), anti-C (27.2), SP (13.6)	
CCP: 74.0; RIS: 60.6	Japanese (100)	CCP	96	Range: 25–300; flexible	AP (8.3), AX (25.0), anti-C (53.1), SP (71.9)	Response rate (FGIR): CCP=RIS
		RIS	104	Range: 1–12; flexible	AP (8.7), AX (23.1), anti-C (40.4), SP (67.3)	
CCP: 38.5; SUL: 30.8	Japanese (100)	CCP	26	Range: 25–900; flexible	AX (NR), anti-C (23.1), SP (NR)	Response rate (FGIR): CCP=SUL
		SUL	26	Range: 200–1,400; flexible	AX (NR), anti-C (34.6), SP (NR)	
MOS: 71; ARI: 63	Japanese (100)	MOS	118	(45–180) flexible	AP (5.9), AX (28.0), anti-C (57.6), SP (89.0)	Response rate (FGIR): MOS=ARI
		ARI	120	(6–24) flexible	AP (6.7), AX (18.3), anti-C (26.7), SP (83.3)	

(*continued*)

Table 1 (*Continued*)

Study	Comparators	Total n	Patients (%)	Diagnosis	Duration	Age, mean ± SD (range)
Kato et al[18], double-blinded, industry	CCP	205	Inpatients and outpatients. Exclusion criteria: excitement; stupor; and/or hebephrenia	NR	8 weeks (no washout phase)	(16–64)
Kudo et al[24], double-blinded, industry	HAL	201	Inpatients and outpatients. Exclusion criteria: stupor and/or hebephrenia	NR	12 weeks	(16–64)
Kudo et al[7], double-blinded, industry	PER	161	Inpatients and outpatients. Exclusion criteria: excitement; stupor; and/or hebephrenia	ICD-10 and DSM-III-R	8 weeks (no washout phase)	MOS: 43.4±13.2; PER: 43.2±13.7; (15–65)
Kudo et al[6], double-blinded, industry	QUE	181	Inpatients and outpatients. Exclusion criteria: stupor and/or hebephrenia	ICD-10	8 weeks (no washout phase)	MOS: 45.6±12.1; QUE: 44.0±13.4; (18–64)

Abbreviations: n, number of patients; SD, standard deviation; AP, antipsychotic; NR, not reported; CAR, carpipramine; CFP, clofluperol; max, maximum; anti-C, anticholinergic drugs; GIR, Global Improved Rating; SP, sleeping pills; PBO, placebo; OXY, oxypertine; PEN, penfluridol; PMZ, promethazine; GCJ, Global Comprehensive Judgment; PIM, pimozide; GJ, Global Judgment; CCP, clocapramine; FGIR, Final Global Improvement Rating; BPD, bromperidol; AX, anxiolytics; HAL, haloperidol; PPZ, perphenazine; ICD, International Statistical Classification of Diseases and Related Health Problems; MOS, mosapramine; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; RIS, risperidone; SUL, sulpride; ARI, aripiprazole; PER, perospirone; QUE, quetiapine.

clocapramine, perospirone, and quetiapine). All of the comparators that were included in the meta-analysis of PANSS scores were aripiprazole, perospirone, and quetiapine. Mosapramine was superior to the other pooled antipsychotics in regard to the PANSS positive subscale scores (SMD=–0.22); however, on the PANSS, there were no significant differences in total scores, negative general subscale scores, response rates, or discontinuation rates between mosapramine and the other pooled antipsychotics (Table 4; Supplementary material 4.3). In comparisons with individual antipsychotics, mosapramine was marginally superior to aripiprazole in terms of the PANSS positive subscale scores (SMD=–0.22, *P*=0.06; Supplementary material 4.3) and discontinuation because of inefficacy (OR=0.36; *P*=0.06; Supplementary material 4.3).

With regard to the comparisons of individual side effects between mosapramine and the other pooled antipsychotics, mosapramine was associated with a greater incidence of at least one side effect (OR=1.72; NNH=13), akathisia (OR=1.81; NNH=13), akinesia/bradykinesia (OR=3.82; NNH, not significant), tremors (OR=2.13; NNH=8), rigidity (OR=2.35; NNH=10), at least one extrapyramidal symptom (OR=2.17; NNH=5), gait disturbance (OR=3.04; NNH=11), disturbance in swallowing (OR=4.58; NNH, not significant), increased salivation (OR=2.51; NNH=10), and anticholinergic drug use (OR=1.98; NNH=6) (Table 4; Supplementary material 4.3). Moreover, mosapramine was associated with higher blood prolactin levels than the other pooled antipsychotics (SMD=–1.19; Table 4; Supplementary material 4.3). With regard to comparisons between mosapramine and aripiprazole, mosapramine was associated with greater incidences of powerlessness (OR=6.68; NNH=11), fatigue (OR=5.92; NNH=7), akathisia (OR=2.45; NNH=7), akinesia/bradykinesia (OR=4.56; NNH=6), dyskinesia (OR=4.42; NNH=13), tremor (OR=2.15; NNH=8), rigidity (OR=2.56; NNH=8), at least one extrapyramidal symptom (OR=3.63; NNH=3), disturbance of gait (OR=4.55; NNH=10), increased salivation (OR=3.35; NNH=6), hyperprolactinemia (OR=569.9; NNH=1), and anticholinergic drug use (OR=3.74; NNH=3) (Supplementary material 4.3). Patients on mosapramine also exhibited higher extrapyramidal symptom scale scores (SMD=0.73), blood prolactin levels (SMD=1.27), and total blood cholesterol levels (SMD=0.38) than did patients on aripiprazole (Supplementary material 4.3). However, mosapramine was associated with a lower incidence of weight loss than aripiprazole (OR=0.35; NNH=8; Supplementary material 4.3). Mosapramine was also associated with higher blood prolactin levels than perospirone (SMD=0.72), with a greater incidence of tremors than clocapramine (OR=2.97; NNH=7), and with a greater incidence of constipation than haloperidol (OR=3.79; NNH=14; Supplementary material 4.3). Moreover, compared with quetiapine, mosapramine was associated with greater incidences of akathisia (OR=2.41; NNH=9), akinesia/bradykinesia (OR=4.26; NNH=6), tremors

Male, %	Ethnicity (%)	AP	n	Dose (mg/day)	Concomitant drugs (%)	Efficacy outcomes
MOS: 57.3; CCP: 61.8	Japanese (100)	MOS	103	Max dose: 120; flexible	AP (4.9), AX (3.9), anti-C (27.2), SP (13.6)	Response rate (FGIR): MOS=CCP
		CCP	102	Max dose: 200; flexible	AP (1.0), AX (2.0), anti-C (19.6), SP (10.8)	
MOS: 57.3; HAL: 58.9	Japanese (100)	MOS	98	Max dose: 225; flexible	Anti-C (83.3), SP (71.9)	Response rate (FGIR): MOS=HAL
		HAL	103	Max dose: 13.5; flexible	Anti-C (88.2), SP (61.8)	
MOS: 65.4; PER: 64.1	Japanese (100)	MOS	82	Range: 50–300; flexible	AP (4.9), anti-C (55.6), SP (64.2)	Response rate (FGIR): MOS=PER
		PER	79	Range: 8–48; flexible	AP (6.4), anti-C (41.0), SP (73.1)	
MOS: 61.1; QUE: 63.3	Japanese (100)	MOS	90	Max dose: 300; flexible	AP (11.1), anti-C (62.2), SP (74.4)	Response rate (FGIR): MOS=QUE
		QUE	91	Max dose: 600; flexible	AP (15.6), anti-C (31.1), SP (65.6)	

Table 2 The results of the meta-analysis of carpiramine studies

	Number of comparisons (comparators)	Number of patients	I^2	OR*	95% CI	*P*
Efficacy						
Response rate	4 (CFP, OXY, PEN, PIM)	290	14	1.35	0.67–2.74	0.41
Discontinuation because of inefficacy	3 (CFP, OXY, PIM)	204	0	0.97	0.19–4.81	0.97
Tolerability						
Discontinuation because of all causes	4 (CFP, OXY, PEN, PIM)	290	0	1.07	0.49–2.35	0.87
Discontinuation because of side effects	3 (CFP, OXY, PIM)	204	0	0.79	0.20–3.09	0.73
Individual side effects						
At least one side effect	4 (CFP, OXY, PEN, PIM)	317	0	1.09	0.68–1.74	0.72
Headache	3 (OXY, PEN, PIM)	227	44	0.93	0.16–5.53	0.93
Insomnia	3 (CFP, OXY, PIM)	204	0	1.09	0.62–1.92	0.77
Sleepiness	4 (CFP, OXY, PEN, PIM)	317	0	0.82	0.34–2.02	0.67
Fatigue[a]	3 (OXY, PEN, PIM)	227	62	0.89	0.23–3.36	0.86
Akathisia	3 (CFP, OXY, PIM)	259	0	0.63	0.33–1.23	0.17
Dyskinesia	3 (CFP, OXY, PEN)	261	0	0.68	0.19–2.35	0.54
Tremor	3 (CFP, OXY, PIM)	259	0	0.54	0.19–1.59	0.27
Rigidity	2 (CFP, PIM)	146	0	0.64	0.19–2.15	0.47
Parkinsonism	4 (CFP, OXY, PEN, PIM)	317	0	0.66	0.36–1.20	0.17
Eye symptoms	2 (OXY, PEN)	171	0	0.19	0.02–1.75	0.14
Dry mouth	3 (OXY, PEN, PIM)	227	0	0.91	0.43–1.96	0.82
Increased salivation	2 (PEN, PIM)	169	30	0.66	0.17–2.62	0.56
Tachycardia	2 (PEN, PIM)	169	0	1.07	0.37–3.08	0.90
Dizziness	3 (OXY, PEN, PIM)	227	0	0.84	0.23–3.06	0.79
Nausea/vomiting	4 (CFP, OXY, PEN, PIM)	317	0	1.16	0.48–2.82	0.74
Constipation	3 (CFP, PEN, PIM)	259	0	0.98	0.35–2.78	0.97
Diarrhea	3 (CFP, PEN, PIM)	259	0	3.02	0.47–19.5	0.25
Rash	2 (CFP, PIM)	146	51	1.73	0.11–26.6	0.69
Sweating	3 (OXY, PEN, PIM)	227	0	1.94	0.33–11.5	0.46
Decreased appetite	4 (CFP, OXY, PEN, PIM)	317	41	1.15	0.55–2.40	0.71

Notes: *OR<1 favors carpiramine; OR>1 favors other pooled antipsychotics. [a]In individual antipsychotic comparisons, carpipramine was associated with less fatigue than was oxypertine (OR=0.11; 95% CI=0.01–0.98; *P*=0.05; NNH=5, *P*=0.02; number of patients =58).

Abbreviations: OR, odds ratio; CI, confidence interval; CFP, clofluperol; OXY, oxypertine; PEN, penfluridol; PIM, pimozide; NNH, number needed to harm.

Table 3 The results of the meta-analysis of clocapramine studies

	Number of comparisons (comparators)	Number of patients	I^2	OR*	95% CI	*P*
Efficacy						
Response rate	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,144	0	1.12	0.86–1.47	0.39
Discontinuation because of inefficacy	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,145	0	0.77	0.44–1.35	0.36
Tolerability						
Discontinuation because of all causes	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,145	0	0.77	0.53–1.11	0.16
Discontinuation because of side effects	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,145	0	0.78	0.37–1.64	0.51
Individual side effects						
At least one side effect	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	52	1.20	0.83–1.72	0.34
Convulsion	4 (BPD, HAL, MOS, PPZ)	756	2	1.03	0.10–10.3	0.98
Fever	4 (BPD, HAL, MOS, PPZ)	756	0	2.53	0.55–11.6	0.23
Headache[a]	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	0	0.47	0.25–0.85	0.01**
Agitation/anxiety	3 (BPD, RIS)	503	0	1.07	0.60–1.92	0.83
Insomnia	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	0	0.92	0.70–1.22	0.58
Powerlessness	2 (MOS, RIS)	405	0	2.13	0.78–5.84	0.14
Sleepiness	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	34	1.18	0.64–2.20	0.60
Fatigue	6 (BPD, HAL, PPZ, RIS, SUL)	938	0	0.74	0.47–1.17	0.20
Disturbance of consciousness	4 (BPD, HAL, MOS, PPZ)	756	0	0.34	0.05–2.16	0.25
Ataxia	3 (HAL, MOS, PPZ)	588	0	1.45	0.40–5.32	0.57
Akathisia	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	0	0.86	0.63–1.18	0.35
Akinesia/bradykinesia	3 (BPD, MOS, RIS)	573	0	0.81	0.29–2.22	0.68
Dyskinesia	5 (BPD, HAL, MOS, PPZ)	891	0	0.99	0.55–1.77	0.97
Dystonia	4 (HAL, MOS, PPZ, RIS)	788	0	1.95	0.69–5.49	0.21
Mask-like face	2 (BPD, RIS)	335	0	0.62	0.07–5.06	0.65
Tremor[b]	5 (BPD, MOS, RIS, SUL)	760	65	0.73	0.36–1.47	0.38
Rigidity	5 (BPD, MOS, RIS, SUL)	760	57	0.81	0.36–1.81	0.61
Parkinsonism	3 (HAL, PPZ, SUL)	435	0	0.81	0.53–1.23	0.32
Paresthesia	3 (HAL, MOS, PPZ)	588	0	0.33	0.09–1.30	0.11
Eye rolling	2 (BPD, SUL)	220	0	0.34	0.03–3.35	0.36
Blurred vision	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	0	0.99	0.50–1.96	0.98
Speech disturbance	4 (BPD, MOS, RIS, SUL)	625	0	0.86	0.35–2.12	0.74
Swallowing disturbance	2 (BPD, RIS)	335	0	3.86	0.63–23.9	0.15
Dry mouth	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	7	0.73	0.42–1.25	0.25
Increased salivation	5 (BPD, MOS, RIS, SUL)	760	0	1.05	0.65–1.69	0.85
Chest pain	4 (BPD, HAL, MOS, PPZ)	756	0	0.88	0.42–1.85	0.74
Tachycardia/palpitation	5 (BPD, HAL, MOS, PPZ, RIS)	956	0	1.33	0.58–3.04	0.50
Dizziness	6 (BPD, HAL, MOS, PPZ, RIS)	1,091	0	0.78	0.47–1.31	0.35
Nausea/vomiting[c]	6 (BPD, HAL, MOS, PPZ, RIS)	1,091	0	0.76	0.48–1.20	0.24
Constipation	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	44	1.28	0.72–2.29	0.40
Diarrhea	3 (BPD, MOS, RIS)	573	48	0.66	0.03–13.7	0.79
Itching	4 (BPD, HAL, MOS, PPZ)	723	0	0.62	0.19–1.95	0.41

Rash	6 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,008	0	1.48	0.51–4.31	0.47
Sweating	6 (BPD, HAL, MOS, PPZ, RIS)	1,091	29	1.14	0.42–3.11	0.80
Decreased appetite[d]	7 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,143	0	0.57	0.39–0.85	0.005**
Weight gain	5 (BPD, MOS, RIS, SUL)	731	3	1.03	0.41–2.54	0.96
Weight loss	5 (BPD, MOS, RIS, SUL)	731	4	1.32	0.49–3.57	0.58
Dysuria	5 (BPD, HAL, MOS, PPZ, RIS)	956	0	1.20	0.55–2.64	0.64
Use of other additional drugs						
Use of sleeping pills	5 (BPD, HAL, MOS, PPZ, RIS)	957	0	0.98	0.74–1.29	0.86
Use of anti-cholinergic drugs	6 (BPD, HAL, MOS, PPZ, RIS, SUL)	1,009	29	1.01	0.74–1.39	0.93
Use of anxiolytics	5 (BPD, HAL, MOS, PPZ, RIS)	957	0	0.80	0.48–1.35	0.41
Use of additional antipsychotics	5 (BPD, HAL, MOS, PPZ, RIS)	957	10	0.52	0.22–1.22	0.13
Laboratory tests of metabolic side effects						
Abnormal blood total cholesterol level	3 (BPD, MOS, RIS)	493	0	1.36	0.29–6.26	0.70
Positive urine glucose test	2 (MOS, RIS)	358	NA	NE	NE	NA

Notes: *OR<1 favors clocapramine; OR>1 favors other pooled antipsychotics. **Statistically significant. [a]NNH is not significant. [b]In individual antipsychotic comparisons, tremors were less strongly associated with clocapramine than with mosapramine (OR=0.34; 95% CI=0.15–0.77; *P*=0.01; NNH=7, *P*=0.007; number =205). [c]In individual antipsychotic comparisons, nausea and vomiting were less strongly associated with clocapramine than with PPZ (OR=0.38; 95% CI=0.16–0.93; *P*=0.03; NNH=25, *P*=0.03; number =192). [d]NNH is not significant. In individual antipsychotic comparisons, decreases in appetite were less strongly associated with clocapramine than with HAL (OR=0.35; 95% CI=0.16–0.77; *P*=0.009; NNH=7, *P*=0.006; number =191).

Abbreviations: OR, odds ratio; CI, confidence interval; BPD, bromperidol; HAL, haloperidol; MOS, mosapramine; PPZ, perphenazine; RIS, risperidone; SUL, sulpiride; NA, not applicable; NE, not estimable; NNH, number needed to harm.

(OR=3.25; NNH=6), rigidity (OR=7.75; NNH=6), occurrence of at least one extrapyramidal symptom (OR=3.67; NNH=3), disturbance of gait (OR=6.77; NNH=9), disturbance of speech (OR=6.27; NNH=7), disturbance in swallowing (OR=4.89; NNH=13), increased salivation (OR=30.6; NNH=4), and anticholinergic drug use (OR=3.65; NNH=3) (Supplementary material 4.3). Comparisons between quetiapine and mosapramine also showed that mosapramine was associated with higher extrapyramidal symptoms scale scores (SMD=0.33) and higher blood prolactin levels (SMD=1.32). (Supplementary material 4.3). However, although we performed a meta-analysis of other side effects, mosapramine did not outperform other antipsychotics in terms of alleviating these adverse effects in either the pooled or the individual analysis (Table 4; Supplementary material 4.3).

Discussion

To our knowledge, this is the first meta-analysis of RCTs focusing on the efficacy and tolerability of iminodibenzyl class antipsychotic treatment (carpipramine, clocapramine, and mosapramine) for patients with schizophrenia.

In the meta-analysis of carpipramine RCTs, all comparators were FGAs (clofluperol, oxypertine, penfluridol, and pimozide). With regard to the clocapramine RCTs included in the meta-analysis, bromperidol, haloperidol, mosapramine, perphenazine, risperidone, and sulpride were all selected as comparators. Although there were no significant differences in any of the efficacy and safety outcomes between clocapramine and the other pooled antipsychotics, clocapramine was marginally inferior to the pooled SGAs (mosapramine and risperisone) in the subgroup analysis (OR=1.51; *P*=0.06). According to the current meta-analysis and previous meta-analyses, mosapramine and risperisone were associated with greater incidences of extrapyramidal symptoms and hyperprolactinemia than other antipsychotics.[25,26] Because carpipramine and clocapramine did not outperform other pooled antipsychotics in regard to the incidences of extrapyramidal symptoms and hyperprolactinemia, they were considered to be pharmacologically similar to FGAs.

Because mosapramine was selected as a comparator in the clinical Phase III trials of aripiprazole, perospirone, and quetiapine in Japan, the clinical and pharmacological characteristics of morepramine revealed by the meta-analysis of this antipsychotic are significant. Mosapramine was more efficacious for positive symptoms compared with the other pooled antipsychotics (aripiprazole, perospirone, and quetiapine), as revealed by the analysis of the combined data from the RCTs of these three SGA comparators. Moreover, mosapramine

Table 4 The results of the meta-analysis of mosapramine studies

	Number of comparisons (comparators)	Number of patients	I^2	OR or SMD	95% CI	*P*
Efficacy						
PANSS total scores	3 (ARI, PER, QUE)	555	0	–0.12†	–0.29 to 0.04	0.14
PANSS positive subscale scores	3 (ARI, PER, QUE)	555	9	–0.22†	–0.39 to –0.04	0.02**
PANSS negative subscale scores	3 (ARI, PER, QUE)	555	0	0.07†	–0.09 to 0.24	0.40
PANSS general subscale scores	3 (ARI, PER, QUE)	555	0	–0.12†	–0.29 to 0.05	0.15
Response rate	5 (ARI, CCP, HAL, PER, QUE)	966	0	1.01*	0.77–1.34	0.92
Discontinuation due to inefficacy	5 (ARI, CCP, HAL, PER, QUE)	986	0	0.74*	0.42–1.30	0.30
Tolerability						
Discontinuation because of all causes	5 (ARI, CCP, HAL, PER, QUE)	986	9	1.05*	0.76–1.44	0.78
Discontinuation because of side effects	5 (ARI, CCP, HAL, PER, QUE)	986	0	1.33*	0.86–2.05	0.20
Discontinuation because of death	4 (ARI, HAL, PER, QUE)	779	0	1.01*	0.18–5.79	0.99
Discontinuation because of death by suicide	4 (ARI, HAL, PER, QUE)	779	0	0.70*	0.11–4.42	0.71
Individual side effects						
At least one side effect[a]	4 (ARI, CCP, PER, QUE)	782	32	1.72*	1.09–2.70	0.02**
Severe/serious side effects	2 (ARI, PER)	397	42	0.59*	0.09–3.78	0.58
Suicide attempt	3 (ARI, PER, QUE)	577	14	0.73*	0.09–5.59	0.76
Neuroleptic malignant syndrome	3 (ARI, PER, QUE)	577	0	0.56*	0.09–3.44	0.53
Fever	4 (ARI, CCP, PER, QUE)	782	4	0.83*	0.33–2.07	0.69
Headache	5 (ARI, CCP, HAL, PER, QUE)	983	0	0.67*	0.37–1.22	0.19
Anxiety	3 (ARI, PER, QUE)	577	0	0.93*	0.61–1.42	0.74
Depression	3 (ARI, HAL, PER)	598	0	0.69*	0.30–1.59	0.39
Excitement	3 (ARI, PER, QUE)	577	0	0.72*	0.40–1.28	0.26
Insomnia	5 (ARI, CCP, HAL, PER, QUE)	983	0	1.01*	0.74–1.38	0.95
Powerlessness[b]	5 (ARI, CCP, HAL, PER, QUE)	983	61	1.10*	0.49–2.51	0.81
Sleepiness/somnolence	5 (ARI, CCP, HAL, PER, QUE)	983	0	1.53*	0.94–2.47	0.09
Fatigue[c]	3 (ARI, PER, QUE)	577	59	2.21*	0.97–5.02	0.06
Ataxia	2 (CCP, HAL)	406	0	1.65*	0.20–13.5	0.64
Akathisia[d]	5 (ARI, CCP, HAL, PER, QUE)	983	8	1.81*	1.26–2.62	0.001**
Akinesia/bradykinesia[e]	4 (ARI, CCP, HAL, QUE)	824	0	3.82*	2.16–6.76	<0.00001**
Dyskinesia[f]	5 (ARI, CCP, HAL, PER, QUE)	983	33	1.41*	0.63–3.17	0.40
Dystonia	4 (ARI, CCP, PER, QUE)	782	42	2.03*	0.69–5.93	0.20
Tremor[g]	5 (ARI, CCP, HAL, PER, QUE)	983	0	2.13*	1.53–2.96	<0.00001**
Rigidity[h]	5 (ARI, CCP, HAL, PER, QUE)	983	27	2.35*	1.47–3.76	0.0004**
Gait disturbance[i]	3 (ARI, PER, QUE)	577	59	3.04*	1.08–8.59	0.04**
At least one extrapyramidal symptoms[j]	4 (ARI, HAL, PER, QUE)	778	76	2.17*	1.19–3.98	0.01**
Extrapyramidal symptoms scales scores[k]	3 (ARI, PER, QUE)	573	85	0.35†	–0.09 to 0.78	0.12
Paresthesia	2 (CCP, HAL)	406	0	1.63*	0.20–13.4	0.65
Eye rolling	2 (HAL, QUE)	381	0	5.75*	0.66–50.2	0.11
Eye symptoms	2 (CCP, HAL)	406	0	0.53*	0.09–3.07	0.47
Speech disturbance[l]	4 (CCP, HAL, PER, QUE)	745	47	2.29*	0.73–7.17	0.16
Swallowing disturbance[m]	3 (HAL, PER, QUE)	540	0	4.58*	1.28–16.4	0.02**
Dry mouth	5 (ARI, CCP, HAL, PER, QUE)	983	0	1.16*	0.68–1.99	0.58
Increased salivation[n]	5 (ARI, CCP, HAL, PER, QUE)	983	69	2.51*	1.06–5.94	0.04**
Chest pain	2 (CCP, PER)	364	0	1.82*	0.48–6.93	0.38
Palpitation	5 (ARI, CCP, HAL, PER, QUE)	983	0	1.91*	0.76–4.80	0.17
QTc prolongation	2 (ARI, QUE)	377	NA	0.33*	0.01–8.12	0.49
Bradycardia	2 (PER, QUE)	339	0	0.32*	0.03–3.14	0.33
Hypertension	2 (PER, QUE)	339	0	3.92*	0.43–35.8	0.23
Hypotension	2 (PER, QUE)	339	0	0.49*	0.12–2.04	0.33
Dizziness/lightheadedness	5 (ARI, CCP, HAL, PER, QUE)	983	4	1.25*	0.72–2.16	0.42
Nausea/vomiting	5 (ARI, CCP, HAL, PER, QUE)	893	0	1.16*	0.65–2.07	0.61
Constipation[o]	5 (ARI, CCP, HAL, PER, QUE)	893	26	1.12*	0.65–1.91	0.69
Diarrhea	2 (CCP, QUE)	385	NA	0.33*	0.01–8.20	0.50
Epigastric distress/abdominal pain	3 (ARI, PER, QUE)	577	16	1.38*	0.59–3.20	0.46
Itching	2 (CCP, HAL)	405	0	3.09*	0.32–30.0	0.33
Sweating	5 (ARI, CCP, HAL, PER, QUE)	983	0	1.55*	0.77–3.14	0.22

(*continued*)

Table 4 (*Continued*)

	Number of comparisons (comparators)	Number of patients	I^2	OR or SMD	95% CI	*P*
Increased appetite	3 (CCP, PER, QUE)	544	0	0.98*	0.28–3.44	0.98
Decreased appetite	5 (ARI, CCP, HAL, PER, QUE)	983	10	1.33*	0.81–2.18	0.25
Weight gain	4 (ARI, CCP, PER, QUE)	725	0	1.39*	0.53–3.63	0.50
Weight loss[p]	5 (ARI, CCP, HAL, PER, QUE)	926	33	0.57*	0.16–2.06	0.39
Change of body weight	3 (ARI, PER, QUE)	524	0	0.15†	–0.02 to 0.33	0.08
Hyperprolactinemia[q]	4 (ARI, HAL, PER, QUE)	741	96	10.9*	0.72–164.9	0.08
Change of blood prolactin level[r]	3 (ARI, PER, QUE)	388	35	1.19†	0.91–1.47	<0.00001**
Dysuria	5 (ARI, CCP, HAL, PER, QUE)	983	0	2.81*	0.98–8.04	0.05
Use of other additional drugs						
Use of sleeping pills	5 (ARI, CCP, HAL, PER, QUE)	980	17	1.28*	0.91–1.80	0.15
Use of anticholinergic drugs[s]	5 (ARI, CCP, HAL, PER, QUE)	980	75	1.98*	1.11–3.53	0.02**
Use of additional antipsychotics	4 (ARI, CCP, PER, QUE)	782	0	0.87*	0.49–1.55	0.63
Laboratory tests of metabolic side effects						
Change of blood total cholesterol level[t]	3 (ARI, PER, QUE)	541	75	0.07†	–0.27 to 0.41	0.68
Positive glucose urine test	5 (ARI, CCP, HAL, PER, QUE)	890	0	0.56*	0.17–1.86	0.34

Notes: †Negative SMD values favor mosapramine; positive SMD values favor other pooled antipsychotics. *OR<1 favors mosapramine; OR>1 favors other pooled antipsychotics. **Statistically significant. [a]NNH=13, *P*=0.05. In individual antipsychotic comparisons, patients on mosapramine were more likely to have at least one side effect than were patients on QUE (OR=2.73; 95% CI=1.09–2.70; *P*=0.02; NNH=5, *P*=0.002; number =180). [b]In individual antipsychotic comparisons, powerlessness was associated more strongly with mosapramine than with ARI (OR=6.68; 95% CI=1.46–30.5; *P*=0.01; NNH=11, *P*=0.005; number =238). [c]In individual antipsychotic comparisons, fatigue was more strongly associated with mosapramine than with ARI (OR=5.92; 95% CI=1.96–17.9; *P*=0.002; NNH=7, *P*=0.0004; number =238). [d]NNH=13, *P*=0.0004. In individual antipsychotic comparisons, akathisia was more strongly associated with mosapramine than with ARI (OR=2.45; 95% CI=1.28–4.70; *P*=0.007; NNH=7, *P*=0.005; number =238) and with QUE (OR=2.41; 95% CI=1.02–5.65; *P*=0.04; NNH=9, *P*=0.04; number =180). [e]NNH is not significant. In individual antipsychotic comparisons, akinesia/bradykinesia was associated more strongly with mosapramine than with ARI (OR=4.56; 95% CI=1.89–11.0; *P*=0.0007; NNH=6, *P*=0.0002; number =238) and QUE (OR=4.26; 95% CI=1.63–11.2; *P*=0.003; NNH=6, *P*=0.001; number =180). [f]In individual antipsychotic comparisons, dyskinesia was associated more strongly with mosapramine than with ARI (OR=4.42; 95% CI=1.21–16.1; *P*=0.02; NNH=13, *P*=0.01; number =238). [g]NNH=8, *P*<0.00001. In individual antipsychotic comparisons, tremors were more strongly associated with mosapramine than with ARI (OR=2.15; 95% CI=1.14–4.05; *P*=0.02; NNH=8, *P*=0.02; number =238), CCP (OR=2.97, 95% CI=1.30–6.79; *P*=0.01; NNH=7, *P*=0.007; number =205), and QUE (OR=3.25; 95% CI=1.46–7.23; *P*=0.004; NNH=6, *P*=0.002; number =180). [h]NNH=10, *P*<0.0001. In individual antipsychotic comparisons, rigidity was associated more strongly with mosapramine than with ARI (OR=2.56; 95% CI=1.25–5.23; *P*=0.01; NNH=8, *P*=0.008; number =238) and QUE (OR=7.75; 95% CI=2.21–27.3; *P*=0.001; NNH=6, *P*=0.0002; number =180). [i]NNH=11, *P*<0.0001. In individual antipsychotic comparisons, disturbance of gait was more strongly associated with mosapramine than with ARI (OR=4.55; 95% CI=1.47–14.1; *P*=0.008; NNH=10, *P*=0.004; number =238) and QUE (OR=6.77; 95% CI=1.47–31.2; *P*=0.01; NNH=9, *P*=0.004; number =180). [j]NNH=5, *P*=0.01. In individual antipsychotic comparisons, mosapramine was more strongly associated with at least one extrapyramidal symptom than were ARI (OR=3.63; 95% CI=2.12–6.20; *P*<0.00001; NNH=3, *P*<0.00001; number =238) and QUE (OR=3.67; 95% CI=1.97–6.81; *P*<0.0001; NNH=3, *P*<0.0001; number =180). [k]In individual antipsychotic comparisons, higher extrapyramidal symptom scale scores were more likley to be associated with mosapramine than with ARI (SMD=0.73; 95% CI=0.47–0.90; *P*<0.00001; number =234) and QUE (SMD=0.33; 95% CI=0.04–0.62; *P*=0.03; number =180). [l]For individual antipsychotic comparisons, disturbance of speech was associated more strongly with mosapramine than with QUE (OR=6.27; 95% CI=1.76–22.4; *P*=0.005; NNH=7, *P*=0.001; number =180). [m]NNH is not significant. In individual antipsychotic comparisons, disturbance of swallowing was associated more strongly with mosapramine than with QUE (OR=4.89; 95% CI=1.03–23.3; *P*=0.05; NNH=13, *P*=0.03; number =180). [n]NNH=10, *P*=0.04. In individual antipsychotic comparisons, increased salivation was associated more strongly with mosapramine than were ARI (OR=3.35; 95% CI=1.63–6.89; *P*=0.001; NNH=6, *P*=0.0005; number =238) and QUE (OR=30.6; 95% CI=4.02–231.9; *P*=0.0009; NNH=4, *P*<0.00001; number =180). [o]In individual antipsychotic comparisons, constipation was associated more strongly with mosapramine than with HAL (OR=3.79; 95% CI=1.01–14.2; *P*=0.05; NNH=14, *P*=0.04; number =201). [p]In individual antipsychotic comparisons, weight loss was associated less strongly with mosapramine than with ARI (OR=0.35; 95% CI=0.16–0.77; *P*=0.009; NNH=8, *P*=0.006; number =238). [q]In individual antipsychotic comparisons, hyperprolactinemia was associated more strongly with mosapramine than with ARI (OR=569.9; 95% CI=117.9–2,753.6; *P*<0.00001; NNH=1, *P*<0.00001; number =201). [r]In individual antipsychotic comparisons, a change in blood prolactin level was more highly associated with mosapramine than with ARI (SMD=1.27; 95% CI=0.97–1.58; *P*<0.00001; number =201), PER (SMD=0.72; 95% CI=0.11–1.32; *P*=0.02; number =45), and QUE (SMD=1.32; 95% CI=0.96–1.68; *P*<0.00001; number =142). [s]NNH=6, *P*=0.04. In individual antipsychotic comparisons, the use of anticholinergic drugs was associated more strongly with mosapramine than with ARI (OR=3.74; 95% CI=2.17–6.45; *P*<0.00001; NNH=3, *P*<0.00001; number =238) and QUE (OR=3.65; 95% CI=1.97–6.76; *P*<0.0001; NNH=3, *P*<0.0001; number =180). [t]In individual antipsychotic comparisons, a higher change of total blood cholesterol level was associated with mosapramine than with ARI (SMD=0.38; 95% CI=0.11–0.64; *P*=0.005; number =226).

Abbreviations: OR, odds ratio; SMD, standardized mean difference; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale; ARI, aripiprazole; PER, perospirone; QUE, quetiapine; CCP, clocapramine; HAL, haloperidol; NA, not applicable; NNH, number needed to harm.

was marginally superior to aripiprazole in terms of PANSS positive subscale scores and discontinuation due to inefficacy (OR=0.36; *P*=0.06). However, mosapramine was associated with greater incidences of extrapyramidal symptoms and hyperprolactinemia than the other antipsychotics were. Moreover, mosapramine was associated with a marginally higher incidence of weight gain than the other pooled antipsychotics (SMD=0.15; *P*=0.08). Given these results, although mosapramine may be more efficacious than the other antipsychotics, it does require cautious use with respect to side effects. Therefore, we recommend that mosapramine should not be used as a first-line agent for first-episode patients. Because the D_2 receptor/5-HT_2 receptor occupancy ratios of clocapramine (3) and of mosapramine (7.4) were lower than the ratio of clozapine (49),[1] the pharmacological profile of clocapramine and mosapramine seemed to be clinically similar to that of FGAs, even though carpipramine was classified as an SGA.

Limitations

There are several limitations to our findings. First, as discussed previously in this article, the limitation of this study was the paucity of included studies and the small sample size. Second, although we aggregated data from studies of each iminodibenzyl class antipsychotic to obtain greater statistical power and overcome the limitation of sample size, the comparators do have several differences in their pharmacological profiles. The third limitation was that our study had several differences in patient populations (ie, some were inpatients and some were outpatients). Moreover, although all studies were clinical Phase III trials in Japan, most studies included in the meta-analysis used additional antipsychotics during the trial, which could confound the results of their meta-analyses (Table 1). Finally, all studies included in our meta-analysis had short trial durations ranging from 8–12 weeks. Because the objectives of adjuvant therapy are to gain further efficacy in the reduction of symptoms and to maintain adherence to the concurrent main antipsychotic, further research will be required to elucidate the long-term efficacy and tolerability of iminodibenzyl class antipsychotics in patients with schizophrenia.

Conclusion

In conclusion, our results suggest that the pharmacological profiles of carpipramine and clocapramine, which are classified as SGAs, were similar to those of FGAs because there were no significant differences in efficacy and safety outcomes. However, mosapramine was associated with higher risks of extrapyramidal symptoms and hyperprolactinemia than the other SGAs, although this drug may be beneficial for the improvement of positive symptoms.

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