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

Neuropsychiatric Disease and Treatment 2014:10 2339–2351

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Original Research

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This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
10 December 2014
Number of times this article has been viewed
and meta-analysis can overcome the limitations of small studies and cover broader outcome measures.

Iminodibenzyl class antipsychotics are structurally related to both tricyclic antidepressants such as imipramine, and butyrophenones such as haloperidol. Although carpipramine is available in both Japan and France, clozapramine 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 clozapramine to striatal dopamine D₂ receptors and frontal serotonin (5-HT₂) receptors in a rat brain, clozapramine and mosapramine exhibited potency in occupying the D₂ receptors and 5-HT₂ receptors. On the basis of this evidence, clozapramine and mosapramine are classified as second-generation antipsychotics (SGAs). However, the D₂ receptor/5-HT₂ receptor occupancy ratios of clozapramine (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). 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. Carpipramine is also classified as an SGA because it was reported to exhibit a D₂ receptor/5-HT₂ receptor antagonist effect. However, the D₂ receptor/5-HT₂ 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, clozapramine, 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). We performed a systematic literature review according to the Patient Intervention Comparator Outcome strategy (patients: schizophrenia; intervention: carpipramine, clozapramine, 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, clozapramine, 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 “clozapramine” 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; clozapramine, 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 clozapramine 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) 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\textsuperscript{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\textsuperscript{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,\textsuperscript{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:

$$\text{NNH} = \frac{1}{\text{RD}}$$

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 $\geq 50\%$ to reflect considerable heterogeneity.\textsuperscript{13} In cases of $I^2$ values that were $\geq 50\%$ 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\textsuperscript{14–17} in the meta-analysis for carpipramine, six\textsuperscript{18–23} for clocapramine, and five\textsuperscript{5–7,18,24} for mosapramine (Table 1). Other than the Yamagami et al study,\textsuperscript{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,\textsuperscript{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, haloperidol, perphenazine, and sulpride) and SGAs (mosapramine and risperidone). Carpipramine did not differ from other pooled antipsychotics 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 al17, 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 Kaneko14, 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 al12, 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 al14, 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 al12, 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 al22, 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 al23, 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 al18, 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 al19, 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 al20, single-blinded, nonindustry | SUL         | 52      | Exclusion criteria: stupor and/or hebephrenia | NR        | 8 weeks (no washout phase) | (18–59) |
| **MOS studies** |             |         |              |           |          |                        |
| 031-95-003, double-blinded, industry | ARJ         | 238     | Schizophrenia | ICD-10    | 8 weeks | MOS: 45.2±12.7; ARJ: 45.5±12.4 (16–65) |
| Male, % | Ethnicity (%) | AP | n   | Dose (mg/day)                      | Concomitant drugs (%) | Efficacy outcomes          |
|--------|-------------|----|-----|-----------------------------------|-----------------------|---------------------------|
| CAR: 66.7 | Japanese (100) | CAR | 45  | Mean dose: NR; max dose: 300; flexible | Anti-C (NR), SP (NR)  | Response rate             |
| CFP: 62.2 |             | CFP | 45  | Mean dose: NR; max dose: 6; flexible | Anti-C (NR), SP (NR)  | (GIR): CAR=CFP           |
| CAR: 34.4 | Japanese (100) | CAR | 29  | Mean dose: NR; max dose: 200; fixed | NR                    | Response rate             |
| OXY: 34.4 |             | OXY | 29  | Mean dose: NR; max dose: 240; flexible | NR                    | (GIR): CAR=OXY            |
| CAR: 77.3 | Japanese (100) | CAR | 42  | Mean dose: NR; max dose: 200; fixed | PMZ (100)             | Response rate             |
| PEN: 66.7  |             | PEN | 44  | Mean dose: NR; max dose: 80; fixed | PMZ (100)             | (GC): CAR=PEN            |
| CAR: 50.0 | Japanese (100) | CAR | 28  | Mean dose: NR; range: 75–200; flexible | Anti-C (NR), SP (NR)  | Response rate             |
| PIM: 50.0  |             | PIM | 28  | Mean dose: NR; range: 3–8; flexible | Anti-C (NR), SP (NR)  | (GJ): CAR=PIM            |
| CCP: 50.6 | 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             |
| BPD: 58.0  |             | 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) | (FGIR): CCP=BPD          |
| CCP: 51.4 | Japanese (100) | CCP | 70  | Mean dose: NR; range: 25–225; flexible | AP (NR), AX (NR), anti-C (NR), SP (NR) | Response rate             |
| BPD: 52.3  |             | BPD | 66  | Mean dose: NR; range: 2–18; flexible | AP (NR), AX (NR), anti-C (NR), SP (NR) | (FGIR): CCP=BPD          |
| CCP: 56.7 | Japanese (100) | CCP | 97  | Mean dose: 173.2; range: 75–225; flexible | AP (0.0), AX (1.0), anti-C (60.8), SP (46.4) | Response rate             |
| HAL: 57.4, |             | HAL | 94  | Mean dose: 7.2; range: 1–9; flexible | AP (3.2), AX (4.3), anti-C (61.7), SP (50.0) | (FGIR): CCP=HAL=PPZ      |
| PPZ: 53.7  |             | PPZ | 95  | Mean dose: 21.6; range: 3–27; flexible | AP (4.2), AX (1.1), anti-C (53.7), SP (49.5) | Response rate             |
| CCP: 56.7 | Japanese (100) | CCP | 102 | Max dose: 200; flexible             | AP (1.0), AX (2.0), anti-C (19.6), SP (10.8) | Response rate             |
| MOS: 57.3  |             | MOS | 103 | Max dose: 120; flexible             | AP (4.9), AX (3.9), anti-C (27.2), SP (13.6) | (FGIR): CCP=MOS          |
| CCP: 74.0 | Japanese (100) | CCP | 96  | Range: 25–300; flexible             | AP (8.3), AX (25.0), anti-C (53.1), SP (71.9) | Response rate             |
| RIS: 60.6  |             | RIS | 104 | Range: 1–12; flexible              | AP (8.7), AX (23.1), anti-C (40.4), SP (67.3) | (FGIR): CCP=RIS          |
| CCP: 38.5 | Japanese (100) | CCP | 26  | Range: 25–900; flexible             | AX (NR), anti-C (23.1), SP (NR) | Response rate             |
| SUL: 30.8  |             | SUL | 26  | Range: 200–1,400; flexible          | AX (NR), anti-C (34.6), SP (NR) | (FGIR): CCP=SUL          |
| MOS: 71; | Japanese (100) | MOS | 118 | (45–180) flexible                  | AP (5.9), AX (28.0), anti-C (57.6), SP (89.0) | Response rate             |
| ARI: 63    |             | ARI | 120 | (6–24) flexible                    | AP (6.7), AX (18.3), anti-C (26.7), SP (83.3) | (FGIR): MOS=ARI          |
|          |             |     |     |                                   |                       | (continued)               |
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 = 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

### Table 1 (Continued)

| Study                | Comparators | Total n | Patients (%) | Diagnosis | Duration | Age, mean ± SD (range) |
|----------------------|-------------|---------|--------------|-----------|----------|------------------------|
| Kato et al<sup>a</sup>, 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<sup>b</sup>, double-blinded, industry | HAL         | 201     | Inpatients and outpatients. Exclusion criteria: stupor and/or hebephrenia | NR        | 12 weeks | (16–64)               |
| Kudo et al<sup>c</sup>, 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<sup>d</sup>, 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, carpiopamine; CFP, clofuhperol; max, maximum; anti-C, anticholinergic drugs; GIR, Global Improved Rating; SP, sleeping pills; PBO, placebo; OXY, oxyperitine; PEN, penfluridol; PMZ, promethazine; GCJ, Global Comprehensive Judgment; PIM, pimozide; GJ, Global Judgment; CCP, clocapramine; FGR, Final Global Improvement Rating; BPD, bromperidol; AX, anxiolytics; HAL, haloperidol; PFZ, 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.
Table 2 The results of the meta-analysis of carpiramine studies

| Number of comparisons (comparators) | Number of patients | I² | 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                             | 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 |
| Rigidty                             | 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 | 0.89 |
| 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. In individual antipsychotic comparisons, carpiramine 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

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

| Use of sleeping pills | 5 (BPD, HAL, MOS, PZ, RIS) | 957 | 0 | 0.98 | 0.74–1.29 | 0.86 |
|----------------------|-----------------------------|------|----|-------|------------|------|
| Use of anxiolytics   | 5 (BPD, HAL, MOS, PZ, RIS) | 957 | 0 | 0.80 | 0.48–1.35 | 0.41 |
| Use of additional antipsychotics | 5 (BPD, HAL, MOS, PZ, RIS) | 957 | 10 | 0.52 | 0.22–1.22 | 0.13 |

Laboratory tests of metabolic side effects

| Abnormal total cholesterol level | 3 (BPD, MOS, RIS) | 493 | 0 | 1.36 | NA | NE |
|---------------------------------|------------------|------|----|-------|----|----|

Notes:
- Statistically significant. NNH not significant.
- *Or favors other pooled antipsychotics. **Statistically significant.
- 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.

*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.

Discussion

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

In the meta-analysis of carpipramine RCTs, all comparators were FGAs (clofuperol, oxyperpine, penfluridol, and pimozide). With regard to the clocapramine RCTs included in the meta-analysis, bromperidol, haloperidol, mosapramine, perphenazine, risperidone, and sulpiride were all selected as comparators. Although there were no significant differences in any of the efficacy and safety outcomes between clozapine and the other pooled antipsychotics, clocapramine was marginally inferior to the pooled SGAs (mosapramine and risperidone) in the subgroup analysis (OR=1.51; P=0.06).

According to the current meta-analysis and previous meta-analyses, mosapramine and risperidone were associated with greater incidences of extrapyramidal symptoms and hyperprolactinemia than other antipsychotics. 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

| Efficacy | Number of comparisons (comparators) | Number of patients | I² | OR or SMD 95% CI | P  |
|----------|-------------------------------------|--------------------|----|-----------------|----|
| 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 | Number of comparisons (comparators) | Number of patients | I² | OR or SMD 95% CI | P  |
|--------------|-------------------------------------|--------------------|----|-----------------|----|
| 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 | 1.13* | 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 | Number of comparisons (comparators) | Number of patients | I² | OR or SMD 95% CI | P  |
|-------------------------|-------------------------------------|--------------------|----|-----------------|----|
| At least one side effect† | 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 | 0.73 |
| 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 |
| Powerlessnessa | 5 (ARI, CCP, HAL, PER, QUE) | 983 | 6 | 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 |
| Fatiguec | 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 |
| Akathisiaa | 5 (ARI, CCP, HAL, PER, QUE) | 983 | 8 | 1.81* | 1.26–2.62 | 0.001** |
| Akinesia/bradykinesiaa | 4 (ARI, CCP, HAL, QUE) | 824 | 0 | 3.82* | 2.16–6.76 | <0.00001** |
| Dysskinesiaa | 5 (ARI, CCP, HAL, PER, QUE) | 983 | 33 | 1.41* | 0.63–3.17 | 0.40 |
| Dyskinesiaa | 5 (ARI, CCP, HAL, PER, QUE) | 983 | 6 | 1.10* | 0.49–2.51 | 0.81 |
| Dystonia | 4 (ARI, CCP, PER, QUE) | 782 | 0 | 2.03* | 0.69–5.93 | 0.20 |
| Rigidityb | 5 (ARI, CCP, HAL, PER, QUE) | 983 | 27 | 2.35* | 1.47–3.76 | 0.0004** |
| Gait disturbancec | 3 (ARI, PER, QUE) | 577 | 59 | 3.04* | 1.08–8.59 | 0.04** |
| At least one extrapyramidal symptomsj | 4 (ARI, HAL, PER, QUE) | 778 | 76 | 2.17* | 1.19–3.98 | 0.01** |
| Extrapyramidal symptoms scales scoresk | 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 | 0.57* | 0.66–50.2 | 0.11 |
| Eye symptoms | 2 (CCP, HAL) | 406 | 0 | 0.53* | 0.09–3.07 | 0.47 |
| Speech disturbancec | 4 (CCP, HAL, PER, QUE) | 745 | 47 | 2.29* | 0.73–7.17 | 0.16 |
| Swallowing disturbancec | 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 salivationa | 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 |
| Constipationc | 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)

| Use of other additional drugs              | Number of comparisons (comparators) | Number of patients | OR or SMD 95% CI | P       |
|-------------------------------------------|-------------------------------------|--------------------|-----------------|---------|
| Use of sleeping pills                     | 5 (ARI, CCP, HAL, PER, QUE)         | 980                | 17              | 1.28*   |
| Use of anticholinergic drugs              | 5 (ARI, CCP, HAL, PER, QUE)         | 980                | 75              | 1.98*   |
| Use of additional antipsychotics          | 4 (ARI, CCP, PER, QUE)              | 782                | 0               | 0.87*   |

**Notes:** SMD values favor mosapramine; positive SMD values favor other pooled antipsychotics. *OR<1 favors mosapramine; OR>1 favors other pooled antipsychotics. **Statistically significant. *NHHi=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=1.99–2.70; P=0.002; number =180). 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; NHHi=11, P=0.005; number =238). 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; number =238); NHHi=13, P=0.004. In individual antipsychotic comparisons, akathisia was more strongly associated with mosapramine than with ARI (OR=4.45; 95% CI=2.48–4.70; P=0.007; NHHi=7, P=0.005; number =238) and with QUE (OR=2.41; 95% CI=1.02–5.65; P=0.04; NHHi=9, P=0.04; number =180). NHHi is not significant. In individual antipsychotic comparisons, akathisia/bradykinesia was associated more strongly with mosapramine than with ARI (OR=4.56; 95% CI=1.89–11.0; P=0.007; NHHi=6, P=0.002; number =238) and QUE (OR=9.26; 95% CI=1.63–11.2; P=0.003; NHHi=6, P=0.001; number =180). 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; NHHi=13, P=0.01; number =238). 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; NHHi=8, P=0.02; number =238); CCP (OR=2.97; 95% CI=1.30–6.79; P=0.01; NHHi=7, P=0.007; number =205), and QUE (OR=3.25; 95% CI=1.46–7.23; P=0.02; number =180). NHHi=10, P=0.001. 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; NHHi=8, P=0.008; number =238) and QUE (OR=7.75; 95% CI=2.21–27.3; P=0.001; NHHi=6, P=0.002; number =180). 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; NHHi=10, P=0.004; number =238) and QUE (OR=6.77; 95% CI=1.47–31.2; P=0.01; NHHi=9, P=0.004; number =180). NHHi=5, P=0.01. In individual antipsychotic comparisons, tremor 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; NHHi=3, P=0.00001; number =238) and QUE (OR=3.67; 95% CI=1.97–6.81; P=0.001; NHHi=3, P=0.0001; number =180). In individual antipsychotic comparisons, higher extrapyramidal symptom scale scores were more likely to be associated with mosapramine than with ARI (SMD=0.73; 95% CI=0.47–0.90; P=0.00001; number =238) and QUE (SMD=0.33; 95% CI=0.04–0.62; P=0.03; number =180). 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; NHHi=7, P=0.001; number =180). NHHi is not significant. In individual antipsychotic comparisons, disturbance of swallowing was more strongly associated with mosapramine than with QUE (OR=4.89; 95% CI=1.03–23.3; P=0.05; NHHi=13, P=0.02; number =180). NHHi=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; NHHi=6, P=0.005; number =238) and QUE (OR=3.60; 95% CI=4.02–231.9; P=0.0009; NHHi=4, P=0.0001; number =180). 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; NHHi=14, P=0.04; number =201). 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; NHHi=8, P=0.006; number =238). In individual antipsychotic comparisons, hyperprolactinemia was associated more strongly with mosapramine than with ARI (OR=56.9; 95% CI=117.9–2,753.6; P=0.00001; NHHi=1, P=0.00001; number =201). In individual antipsychotic comparisons, a change in 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). NHHi=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; NHHi=3, P<0.0001; number =238) and QUE (OR=3.65; 95% CI=1.97–7.61; P<0.0001; NHHi=3, P=0.001; number =180). 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, clozapam; HAL, haloperidol; NA, not applicable; NHH, 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 D3 receptor/5-HT receptor occupancy ratios of clozapam (3) and of mosapramine (7.4) were lower than the ratio of clozapine (49),1 the pharmacological profile of clozapam and mosapramine seemed to be clinically similar to that of FGAs, even though cariprazine 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 (i.e., 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.

Acknowledgments
We thank Mitsubishi Tanabe Pharma Co., Ltd. and Yoshitomi Pharma Co., Ltd. for their contributions to parts of the literature search. We also thank Dainippon Sumitomo Pharma Co., Ltd., Otsuka Pharma Co., Ltd., and AstraZeneca Pharma Co., Ltd. for providing data from their studies.

Disclosure
Dr Kishi has received speaker honoraria from Abbott, Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Mitsubishi Tanabe, Tsumura, Novartis, and Pfizer. Dr Matsunaga has received speaker honoraria from Dainippon Sumitomo, Eli Lilly, and Otsuka. Dr Ivata has received speaker honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer. The authors report no other conflicts of interest in this work.

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