Antipsychotic Monotherapy for Major Depressive Disorder: A Systematic Review and Meta-Analysis

Authors
Akira Nishi*, Kyosuke Sawada*, Hiroyuki Uchida, Masaru Mimura, Hiroyoshi Takeuchi

Affiliation
Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

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Correspondence
Hiroyoshi Takeuchi, MD, PhD
Department of Neuropsychiatry
Keio University School of Medicine
35 Shinanomachi
Shinjuku-ku
160-8582 Tokyo
Japan
hirotak@dk9.so-net.ne.jp

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ABSTRACT

Although several randomized controlled trials (RCTs) have compared the effectiveness, efficacy, and safety of antipsychotic monotherapy (APM) versus placebo in patients with major depressive disorder (MDD), no meta-analysis has examined this topic. We conducted a systematic literature search using MEDLINE and Embase to identify relevant RCTs and performed a meta-analysis to compare the following outcomes between APM and placebo: response and remission rates, study discontinuation due to all causes, lack of efficacy, and adverse events, changes in total scores on depression severity scales, and individual adverse event rates. A total of 13 studies were identified, with 14 comparisons involving 3,197 participants that met the eligibility criteria. There were significant differences between APM and placebo in response and remission rates and changes in the primary depression severity scale in favor of APM, and study discontinuation due to adverse events and several individual adverse events in favor of placebo. No significant difference was observed in discontinuation due to all causes. APM could have antidepressant effects in the acute phase of MDD, although clinicians should be aware of an increased risk of some adverse events.

Introduction

Current clinical guidelines for the treatment of the major depressive disorder (MDD) recommend antidepressants as first-choice pharmacological treatment, particularly selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, and mirtazapine [1]. However, a substantial number of patients do not respond to first-line antidepressants. For instance, in the STAR * D trial, only 36.8 % of patients with MDD achieved remission (defined as a total score of ≤ 5 on the Quick Inventory of Depressive Symptomatology – Self-Report) after the first treatment with citalopram [2], and a meta-analysis showed that 37 % of patients with MDD did not respond (defined as > 50 % improvement in symptoms from baseline on depression severity scales) to first-line treatment with various second-generation antidepressants [3]. When first-line treatment is ineffective, several clinical guidelines recommend augmentation with second-generation antipsychotics as the second- or third-line treatment. However, no clinical guidelines recommend antipsychotic monotherapy (APM) for MDD.

The antidepressant effects of antipsychotics have been reported since the 1960s. For example, thioridazine was reported to be effective for depressive mood in patients with schizophrenia [4, 5]. First-generation antipsychotics were used as antidepressants main-

* Both authors contributed equally

ly for mixed anxiety-depressive states [6]. Benzamides, especially sulpiride, has actually been a treatment option for depression [7, 8]. Recently, several randomized controlled trials (RCTs) have compared the effectiveness, efficacy, and safety of APM in patients with MDD. The APMs investigated included amisulpride [9], haloperidol [10], lurasidone [11], olanzapine [12], quetiapine [13–19], sulpiride [20], and ziprasidone [21] versus placebo. While some trials showed a significant effect of APM on MDD, the findings were inconsistent and depended on the type of antipsychotics. Moreover, each drug, except for quetiapine, was investigated in only one trial. To our knowledge, two meta-analyses and two pooled analyses have examined the effect of quetiapine monotherapy for MDD [22–25]; however, no meta-analysis has comprehensively evaluated all types of antipsychotics until now. Therefore, we conducted a systematic review and meta-analysis of RCTs comparing APM and placebo for MDD.

Methods

Literature search and study selection

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26]. The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020155338) (https://www.crd.york.ac.uk/prospero/). We performed a systematic literature search (last search: October 29, 2020) on MEDLINE and Embase databases using the following keywords: "depressi * AND (antipsychotic * OR *all names of existing antipsychotics* [**Supplementary Table 1**])" and with a limitation of "randomized controlled trial." Two authors (A.N. and K.S.) independently selected studies meeting the following eligibility criteria: (a) an original study (i. e., not a protocol, review, meta-analysis, or secondary analysis); (b) an RCT; (c) a study whose participants were diagnosed with MDD (i. e., not a bipolar disorder or schizoaffective disorder) using standard diagnostic criteria; and (d) a study including treatment arms comprising both APM and placebo arms. In studies involving both patients with MDD and dysthymia, we included only those in which more than 50 % of participants had MDD.

Any disagreements about study selection were resolved by consensus with the lead researcher (H.T.). We used the Cochrane risk of bias tool (available at: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) to assess the risk of bias in each included study.

Data extraction

We extracted the following clinical outcome data from the selected studies: (1) demographic and clinical characteristics of the patients (e. g., age, sex, and duration of illness); (2) information on interventions (e. g., antipsychotic type, dose, and formulation); (3) number of patients who achieved response and remission (response and remission criteria were defined in each study as shown in ▶ **Table 1**); (4) number of patients who discontinued the study due to all causes, lack of efficacy, and adverse events; (5) mean ± standard deviation (SD) of changes from baseline to endpoint in total scores on standard depression severity scales (i. e., the Hamilton Depression Rating Scale [HDRS] [27] and Montgomery–Åsberg Depression Rating Scale [MADRS] [28]) and the Clinical Global Impression – Severity scale (CGI-S); (6) mean ± SD of changes from baseline to endpoint in total scores on self-rating scales that were used in more than one study (i. e., Sheehan Disability Scale (SDS) [29] and Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form [Q-LES-Q-SF] [30]); and (7) number of patients who had a specific adverse event. We calculated the SD from the standard error (SE) if needed. If more than one fixed-dose arm of APM was included, we extracted the data for each dose arm.

Any disagreements about data extraction were resolved by discussion with the lead researcher (H.T.). If the report on the study did not provide sufficient data, we contacted the corresponding author in an attempt to obtain additional information; however, we were not able to obtain any additional data.

Data analysis

We performed a meta-analysis using Review Manager (RevMan) version 5.4. We combined and compared the outcome data between APM and placebo, followed by a subgroup analysis for each antipsychotic. When more than one fixed-dose arm of APM was included in a study, the data in the highest- and second-highest-dose arms were included as the main analysis and sensitivity analysis, respectively, because the highest-dose arm was expected to show the highest therapeutic effect. The primary outcome was the response rate. For depression severity scales such as the HDRS and MADRS, we used the scale defined as the primary outcome in each study for the main analysis and combined the data on each scale (i. e., the HDRS or MADRS) for a sensitivity analysis. For individual adverse events, we used the data on each adverse event noted in two or more studies and listed under the exact same term. We did not evaluate individual adverse events by grouping similar categories (e. g., sedation and fatigue) to avoid double-counting overlapped adverse events. For dichotomous and continuous outcomes, pooled estimates of risk ratios (RRs) and standardized mean differences or mean differences, respectively, were calculated with two-sided 95 % confidence intervals (CIs) using a random-effects model. We calculated the number needed to treat (NNT) for the response and remission rates and the number needed to harm (NNH) for individual adverse events based on pooled estimates of absolute risk reduction. Study heterogeneities were quantified using the I^2 statistic, with an $I^2 \geq 50$ % indicating significant heterogeneity. All effect sizes with $P < 0.05$ were considered significant.

Publication bias was assessed using visual inspection of funnel plots for each outcome. Plots without obvious asymmetry indicated a low possibility of significant publication bias.

Finally, we assessed the overall quality of the evidence regarding the effects of APM versus placebo on each clinical outcome according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Handbook (available at http://gdt.guidelinedevelopment.org/app/handbook/handbook.html).

Results

Included studies

A total of 13 studies with 14 comparisons involving 3,197 participants (n = 1,818 for the APM group; n = 1,379 for the placebo group) that met the eligibility criteria were identified (**Supplementary Figure 1**). The characteristics of these studies are summarized in ▶ **Table 1** and **Supplementary Table 2**. Only two studies were published before 2000 [9, 20]. Because one study included two separate comparisons [12], a total of 14 comparisons were included in the meta-analysis. All studies were conducted in a double-blind fashion and examined an oral antipsychotic formulation. Eleven and two studies investigated second- and first-generation antipsychotics, respectively. Almost all studies lasted for 12 weeks or shorter: 6 weeks (three studies), 8 weeks (four studies), 10 weeks (two studies), 11 weeks (one study), and 12 weeks (two studies). One study had a short intervention period of 1 week [10] and one study had a long intervention period of 6 months [9]. In all but two studies, the participants were in their 40s and 50s on average. All studies included patients who had the acute phase of MDD (i. e., not relapse prevention studies) and three studies included patients who had MDD with specific conditions (i. e., psychotic features [12], treatment resistance [13], and mixed state [11]), one study included patients with comorbidity (i. e., fibromyalgia syndrome [18]), and one study included patients with MDD or dysthymia [9]. Mean depression severity scores ranged from 19.9 to 26.6 on the HDRS and from 24.2 to 33.3 on the MADRS, which correspond to moderate-to-severe depression [31–33]. All except for three studies [9, 13, 20], including the two earliest published, defined response as a ≥ 50 % reduction in total scores on the primary depression severity scale. Ten studies defined remission as lower than a certain score on the primary depression scale. Only two studies examining quetiapine included more than one fixed-dose arm of APM [14, 15].

Risk of bias

The results of risk of the bias assessment are shown in **Supplementary Figure 2**. The risks of blinding the outcome assessment and allocation concealment were not clear in almost all studies. The risks of selective reporting were high in about half of the studies because several studies reported only statistical significance without detailed data.

Meta-analysis

Response rate

A significant difference was found in response rates between the APM and placebo groups in favor of the APM group (11 comparisons, n = 2,448, RR = 1.50, 95 % CI = 1.29 to 1.74, P < 0.001, I^2 = 61 %; ▶ **Fig. 1**). The NNT was 5. Evidence quality was moderate.

Remission rate

A significant difference was shown in remission rates between the APM and placebo groups in favor of the APM group (10 comparisons, n = 2,312, RR = 1.57, 95 % CI = 1.26 to 1.95, P < 0.001, I^2 = 55 %; ▶ **Fig. 1**). The NNT was 8. There was no obvious publication bias. Evidence quality was moderate.

Study discontinuation

No significant difference was found in the study discontinuation due to all causes between the APM and placebo groups (14 comparisons, n = 2,684, RR = 1.04, 95 % CI = 0.89 to 1.22, P = 0.62, I^2 = 40 %; ▶ **Fig. 2**). On the other hand, there were significant differences in the study discontinuation due to lack of efficacy in favor of the APM group (12 comparisons, n = 2,609, RR = 0.47, 95 % CI = 0.31 to 0.70, P < 0.001, I^2 = 20 %; ▶ **Fig. 2**) and the study discontinuation due to adverse events in favor of the placebo group (13 comparisons, n = 2,662, RR = 2.47, 95 % CI = 1.86 to 3.29, P < 0.001, I^2 = 0 %; ▶ **Fig. 2**). There were no obvious publication biases. Evidence quality was moderate for the study discontinuation due to all causes and high for the study discontinuation due to lack of efficacy and adverse events.

Depression severity change

Significant differences were found in the total scores on the primary depression severity scale between the APM and placebo groups in favor of the APM group (seven comparisons, n = 1,015, standardized mean difference = − 0.45, 95 % CI = − 0.64 to − 0.25, P < 0.001, I^2 = 51 %; ▶ **Table 2**). Also, there was a significant difference in CGI-S scores between the two groups in favor of the APM group (seven comparisons, n = 1,017, mean difference = − 0.41, 95 % CI = − 0.70 to − 0.12, P = 0.005, I^2 = 75 %; ▶ **Table 2**). Although few studies were included in the analyses, similar results were observed for the total scores on the HDRS-17 (four comparisons, n = 623, mean difference = − 3.34, 95 % CI = − 6.38 to − 0.29, P = 0.03, I^2 = 81 %) and the MADRS (two comparisons, n = 543, mean difference = − 7.52, 95 % CI = − 9.42 to − 5.62, P < 0.001, I^2 = 0 %; ▶ **Table 2**). In terms of self-rating scales, significant differences were found in the total scores on the SDS and Q-LES-Q-SF between the two groups in favor of the APM group (two comparisons, n = 328, mean difference = -3.38, 95 % CI = − 6.22 to − 0.54, P = 0.02, I^2 = 59 %; two comparisons, n = 455, mean difference = 6.74, 95 % CI = 4.03 to 9.45, P < 0.01, I^2 = 0 %, respectively; ▶ **Table 2**). Evidence quality was high for the primary depression severity scale, MADRS, and Q-LES-Q-SF and moderate for the CGI-S, HDRS-17, and SDS.

Individual adverse events

For eight of 23 individual adverse events, the risks were significantly greater in the APM group than in the placebo group: constipation (eight comparisons, n = 2,154, RR = 1.76, 95 % CI = 1.05 to 2.95, P = 0.03, I^2 = 48 %), dizziness (eight comparisons, n = 2,186, RR = 1.50, 95 % CI = 1.03 to 2.18, P = 0.03, I^2 = 52 %), dry mouth (11 comparisons, n = 2,586, RR = 2.83, 95 % CI = 1.92 to 4.17, P < 0.001, I^2 = 64 %), extrapyramidal symptoms (EPS) (two comparisons, n = 650, RR = 2.05, 95 % CI = 1.04 to 4.03, P = 0.04, I^2 = 0 %), fatigue (six comparisons, n = 1,803, RR = 2.29, 95 % CI = 1.32 to 3.97, P = 0.003, I^2 = 21 %), increased appetite (five comparisons, n = 1,493, RR = 1.98, 95 % CI = 1.13 to 3.50, P = 0.02, I^2 = 1 %), sedation (five comparisons, n = 1,626, RR = 5.67, 95 % CI = 3.87 to 8.30, P < 0.001, I^2 = 0 %), and somnolence (seven comparisons, n = 1,849, RR = 3.96, 95 % CI = 2.94 to 5.35, P < 0.001, I^2 = 21 %; **Supplementary Table 3**). Only nasopharyngitis showed a significantly higher risk in the placebo group than in the APM group (two comparisons, n = 619, RR = 0.31, 95 % CI = 0.12 to 0.76, P = 0.01, I^2 = 0 %; **Supplementary Table 3**). For the other adverse events, no significant differences

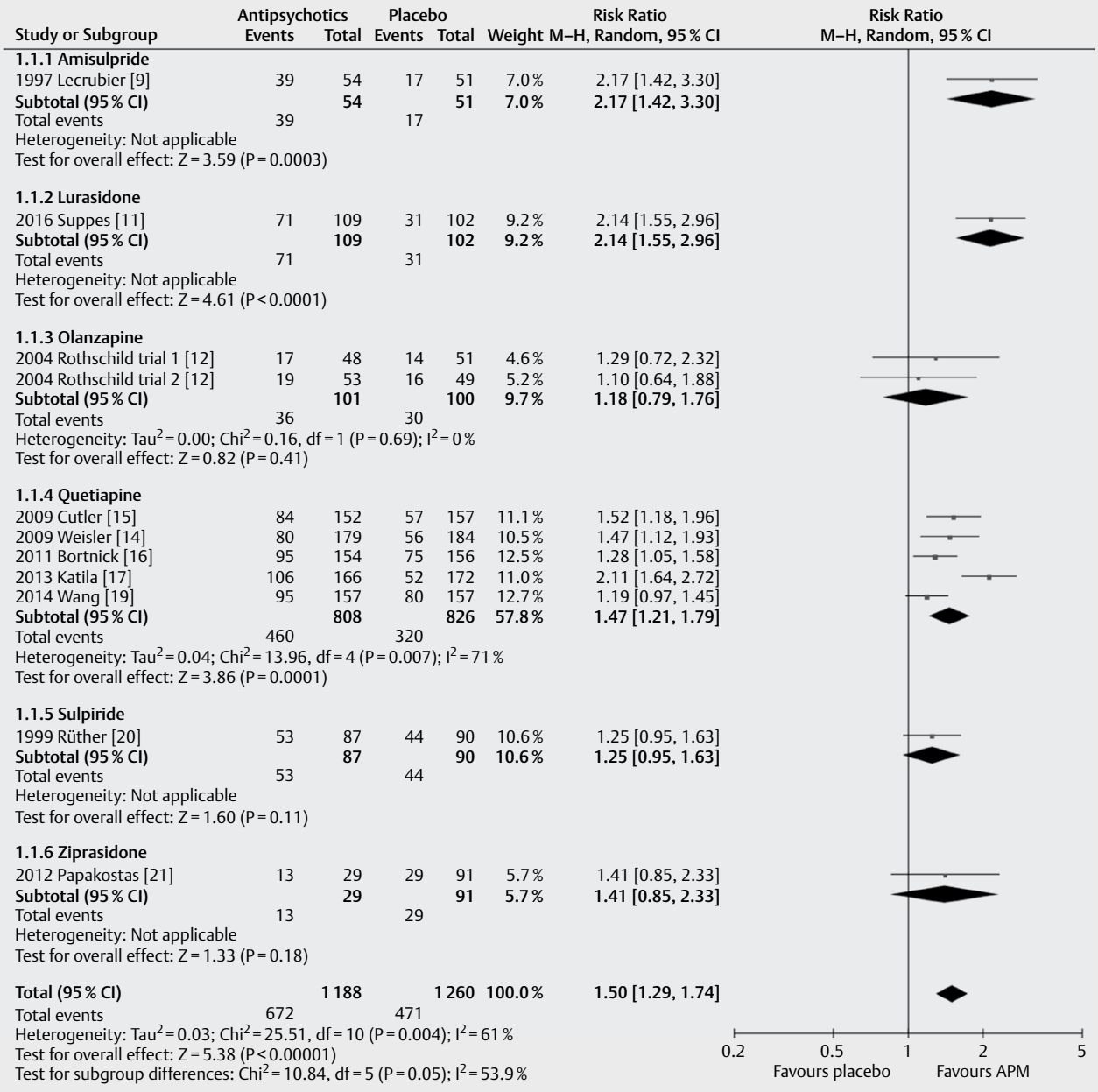
▶ **Table 1** Characteristics of included studies.

Study name	Blinding	Study duration	Total, n	Outpatient, n	Male, n	APM, n	Placebo, n	Age of inclusion criteria, years	Age, years	Diagnosis	Primary depressive severity scale	Response definition	Remission definition	Depression severity scores	Age of onset, years	Antipsychotic treatment: type and dose (range), mg/day	Antipsychotic treatment: duration
1997 Lecrubier [9]	Double-blind	6 months	146	146	61	73	73	N/A	42.4	Primary dysthymia, Dysthymia with MDD, Isolated chronic MDD in partial remission	MADRS	CGI-I score ≤ 2	MADRS total score ≤ 7	MADRS 25.0, CGI-S 5.5	N/A	Amisulpride 50	6 months
1999 Rüther [20]	Double-blind	1 * * + 6 weeks	177	177	N/A	87	90	18–70	50.2	MDD	HDRS-21	CGI-I score ≤ 2	–	N/A	N/A	Sulpiride 181	6 weeks
2004 Rothschild trial 1 [12]	Double-blind	8 weeks	99	0	N/A	48	51	>18	40.7 ± 12.6	MDD with psychotic features	HDRS-24	HDRS-24 total score reduction ≥ 50 %	HDRS-24 total score ≤ 8	N/A	25.4 ± 11.2	Olanzapine 11.9 ± 3.9	8 weeks
2004 Rothschild trial 2 [12]	Double-blind	8 weeks	102	0	N/A	53	49	>18	41.1 ± 10.4	MDD with psychotic features	HDRS-24	HDRS-24 total score reduction ≥ 50 %	HDRS-24 total score ≤ 8	N/A	23.0 ± 12.9	Olanzapine 14.0 ± 4.5	8 weeks
2008 Chaput [13]	Double-blind	12 weeks	22	22	6	11	11	N/A	43.7 ± 11.0	TRD	MADRS, HDRS-21	HDRS-21 total score reduction of ≥ 40 % or a score of < 18	–	HDRS-21 23.0, MADRS 30.7, CGI-S 4.2	22.7 ± 1.3	Quetiapine 148 ± 112	12 weeks
2009 Cutler [15]	Double-blind	8 weeks	461	461	N/A	150 mg/day: 152 300 mg/day: 152	157	18–65	41.6	MDD	MADRS	MADRS total score reduction ≥ 50 %	MADRS total score ≤ 8	N/A	N/A	150 mg/day: Quetiapine XR 125 ± 21 300 mg/day: Quetiapine XR 245 ± 55	6 weeks

▶ **Table 1** Continued

Study name	Blinding	Study duration	Total, n	Outpatient, n	Male, n	APM, n	Placebo, n	Age of inclusion criteria, years	Age, years	Diagnosis	Primary depressive severity scale	Response definition	Remission definition	Depression severity scores	Age of onset, years	Antipsychotic treatment: type and dose (range), mg/day	Antipsychotic treatment: duration
2009 Weisler [14]	Double-blind	8 weeks	723	723	285	50 mg/day: 182 150 mg/day: 178 300 mg/day: 179	184	18–65	40.8	MDD	MADRS	MADRS total score reduction ≥ 50 %	MADRS total score ≤ 8	N/A	N/A	Quetiapine XR 50 or 150 or 300	6 weeks
2011 Bortnick [16]	Double-blind	10 weeks	310	N/A	N/A	154	156	18–65	42.9	MDD	MADRS	MADRS total score reduction ≥ 50 %	MADRS total score ≤ 8	N/A	N/A	Quetiapine XR 150 or 300	8 weeks
2012 Papakostas [21]	Double-blind	12 weeks	120	120	67	29	91	18–65	43.7 ± 11.0	MDD	HDRS-17	HDRS-17 total score reduction ≥ 50 %	HDRS-17 total score ≤ 7	HDRS-17 19.9 ± 5.0, CGI-S 4.3 ± 0.6	N/A	Ziprasidone 81.4 ± 48.3	6 weeks
2013 Katila [17]	Double-blind	11 weeks	338	338	N/A	166	172	>66	71.2	MDD	MADRS	MADRS total score reduction ≥ 50 %	MADRS total score ≤ 8	N/A	N/A	Quetiapine XR 159 * (50–253)	9 weeks
2014 Kennedy [10]	Double-blind	6 weeks	54	54	N/A	27	27	18–65	N/A	MDD	HDRS-17	–	–	N/A	N/A	Haloperidol 0.25	1 week
2014 McIntyre [18]	Double-blind	8 weeks	120	120	4	61	59	18–65	51.0 ± 10.0	MDD with fibromyalgia syndrome	HDRS-17	HDRS-17 total score reduction ≥ 50 %	HDRS-17 total score ≤ 7	HDRS-17 24.8 ± 2.0	N/A	Quetiapine XR 224 (150–300)	8 weeks
2014 Wang [19]	Double-blind	10 weeks	314	314	N/A	157	157	18–65	39.9	MDD	MADRS	MADRS total score reduction ≥ 50 %	MADRS total score ≤ 8	N/A	N/A	Quetiapine XR 140 ± 44	8 weeks
2016 Suppes [11]	Double-blind	6 weeks	211	211	N/A	109	102	18–75	44.9	MDD with mixed state	MADRS	MADRS total score reduction ≥ 50 %	MADRS total score ≤ 12	N/A	N/A	Lurasidone 36.2 (20–60)	6 weeks

* Median, * * Placebo run-in phase; Abbreviations: CGI-S, Clinical Global Impression – Severity scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; TRD, treatment-resistant depression; XR, extended release



▶ **Fig. 1** Response and remission rates; (**a**) Response rate

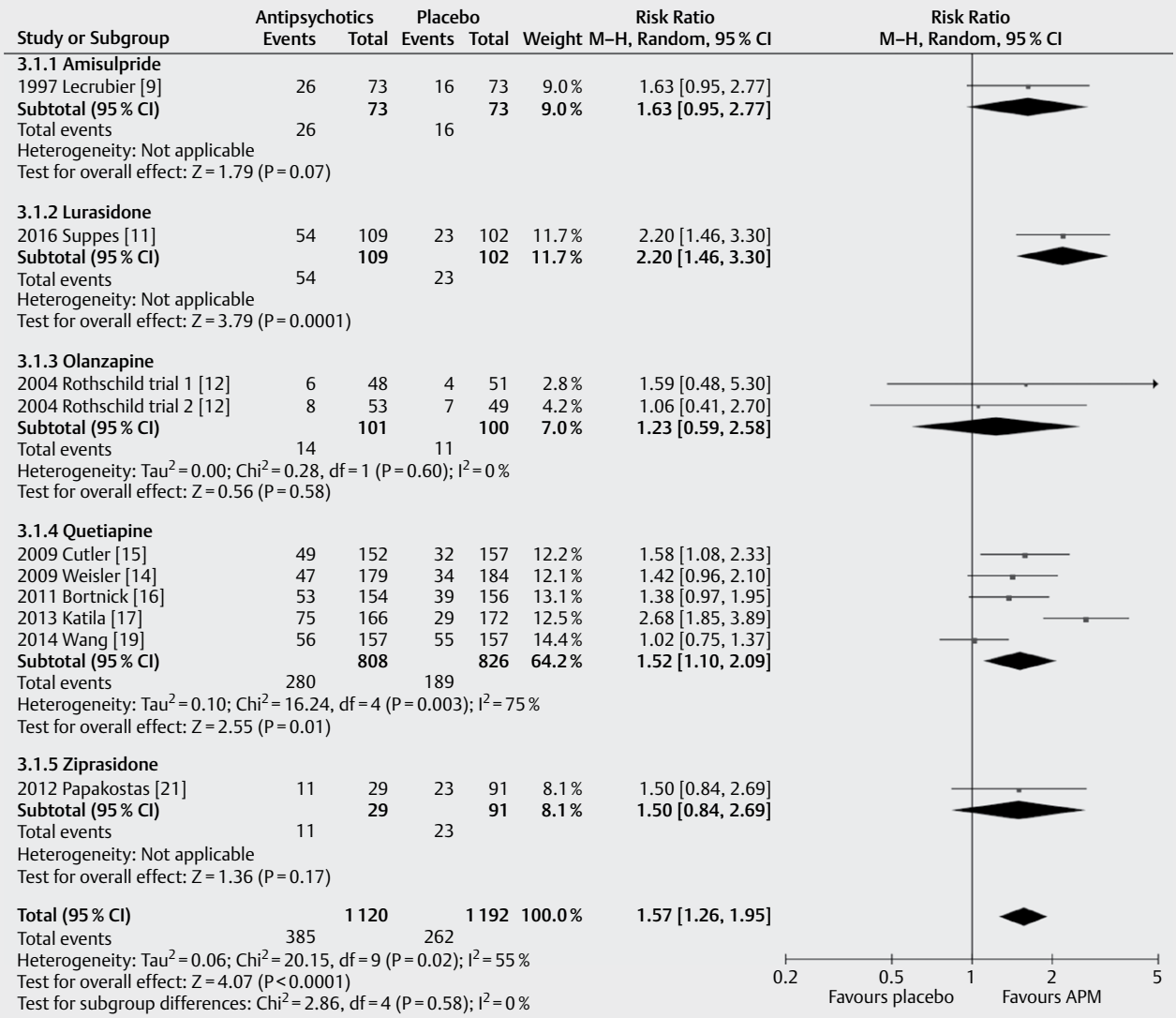
were found (**Supplementary Table 3**). There were no obvious publication biases. The overall quality of evidence was moderate to high.

Sensitivity analyses of studies using quetiapine (150 mg/day)

Two studies examining quetiapine included fixed-dose arms of 300 mg/day and 150 mg/day; therefore, we performed sensitivity analyses of studies using 150 mg/day quetiapine. The significant differences in response rate, remission rate, and study discontinuation were unchanged (**Supplementary Table 4**). In terms of individual adverse events, the significant differences disappeared for constipation and dizziness, and the risk became significantly higher in the APM group than in the placebo group for myalgia (data not shown). We were not able to perform sensitivity analyses on depression severity changes because the studies did not show SD.

Discussion

This meta-analysis revealed significant differences between APM and placebo in response and remission rates and reduction in the primary depression severity scale in favor of APM. Regarding the study discontinuation due to all causes, there was no significant difference between APM and placebo for MDD in the meta-analysis, which may be attributed to the findings that APM was superior

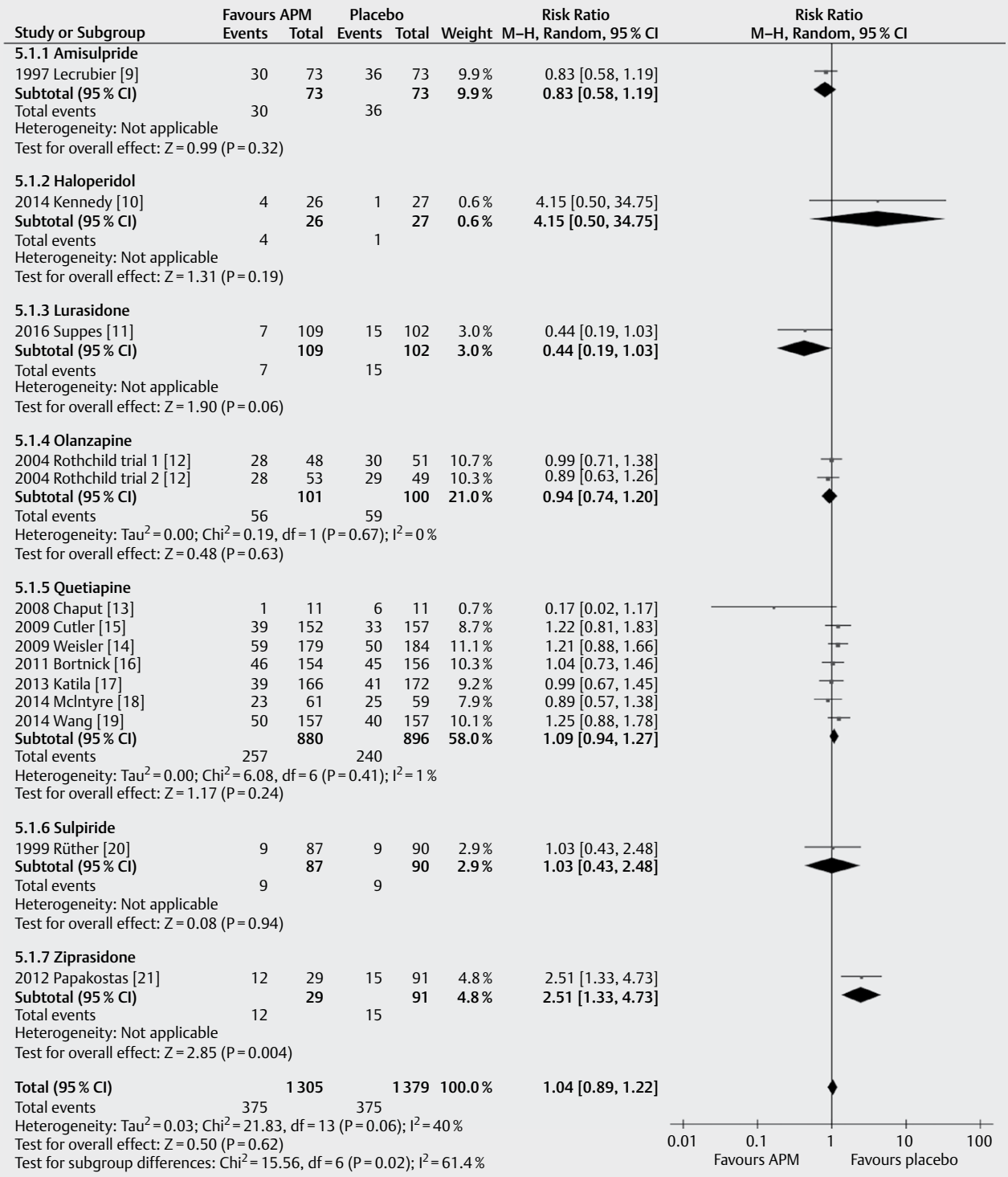


▶ **Fig. 1** Response and remission rates; (**b**) Remission rate

and inferior to placebo for the study discontinuation due to lack of efficacy and adverse events, respectively. In the subgroup analysis of only studies examining quetiapine, significant effectiveness and efficacy of quetiapine were found, which further supports the findings in the previous meta-analysis and pooled analyses [22–25]. The present meta-analysis included additional RCTs and evaluated the risks of individual adverse events, making it superior to past meta-analysis/pooled analyses.

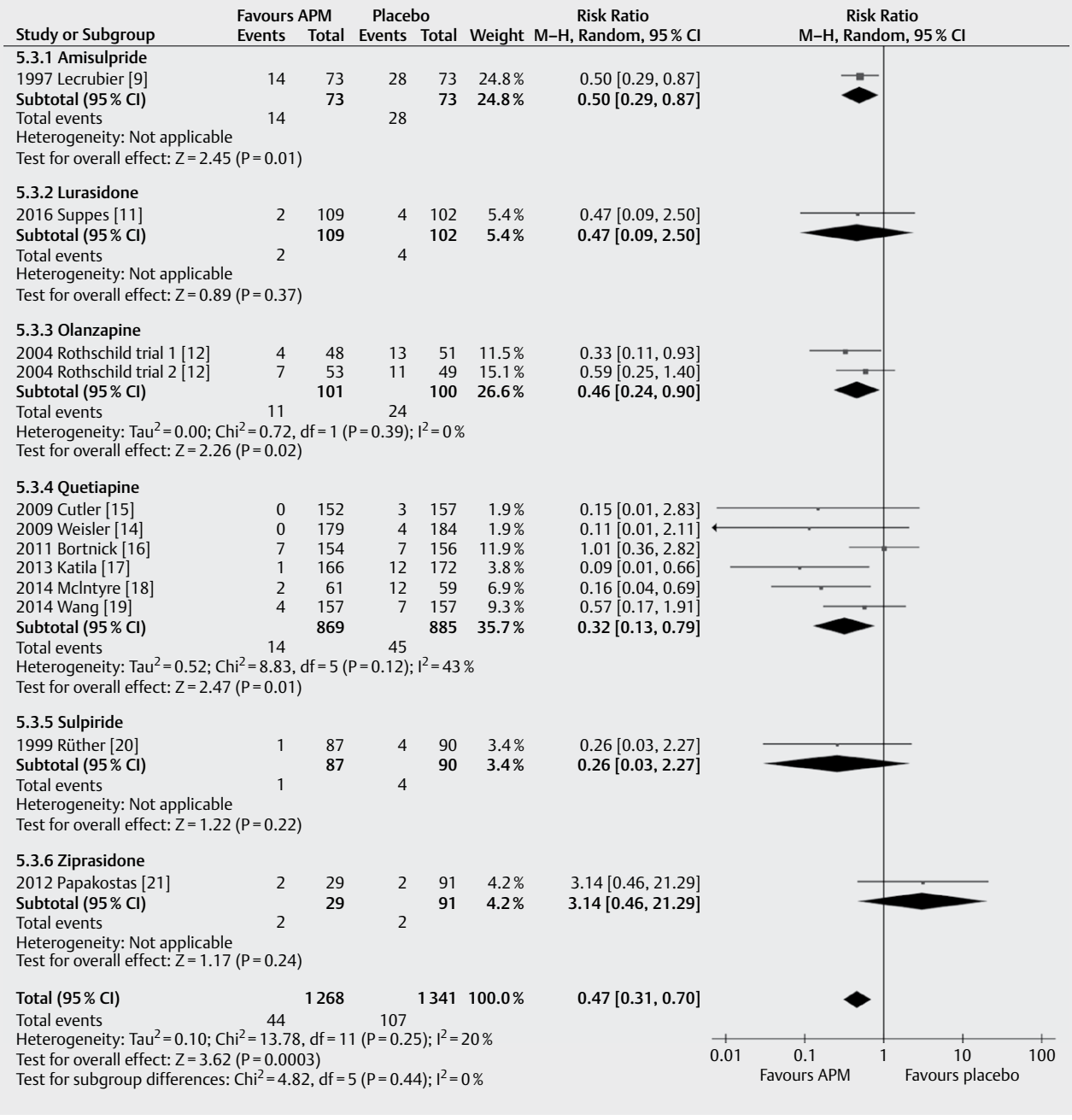
APM showed significantly higher response and remission rates than placebo in this meta-analysis. The NNTs for response and remission rates were 5 and 8, consistent with a previous meta-analysis [34]. The present study found that APM significantly improved depressive symptoms by 3.3 points on the HDRS-17 and 7.5 points on the MADRS in patients with moderate-to-severe MDD compared with placebo. A recent network meta-analysis showed that 21 antidepressants were more effective for the acute treatment of MDD than placebo, with mirtazapine, duloxetine, and venlafaxine showing the highest efficacy [35]. We looked at the score changes in depression rating scales in each included study investigating these three antidepressants because only odds ratios were reported in the network meta-analysis. Interestingly, we found that the score improvements in the HDRS-17 or MADRS for mirtazapine, duloxetine, or venlafaxine were almost the same as those for APM in the present meta-analysis [36–42]. Moreover, two RCTs included in the present meta-analysis demonstrated no differences in efficacy between quetiapine and antidepressants (i. e., duloxetine and escitalopram) [15, 19]. Another RCT also indicated the non-inferiority of amisulpride to paroxetine in terms of efficacy and safety for MDD [43]. These suggest that APM, especially quetiapine, may be a useful treatment for MDD, at least in terms of efficacy, compared with standard treatment with antidepressants.

Compared with placebo, APM significantly increased the risks of study discontinuation due to adverse events. This is consistent with a recent network meta-analysis showing significant differenc-



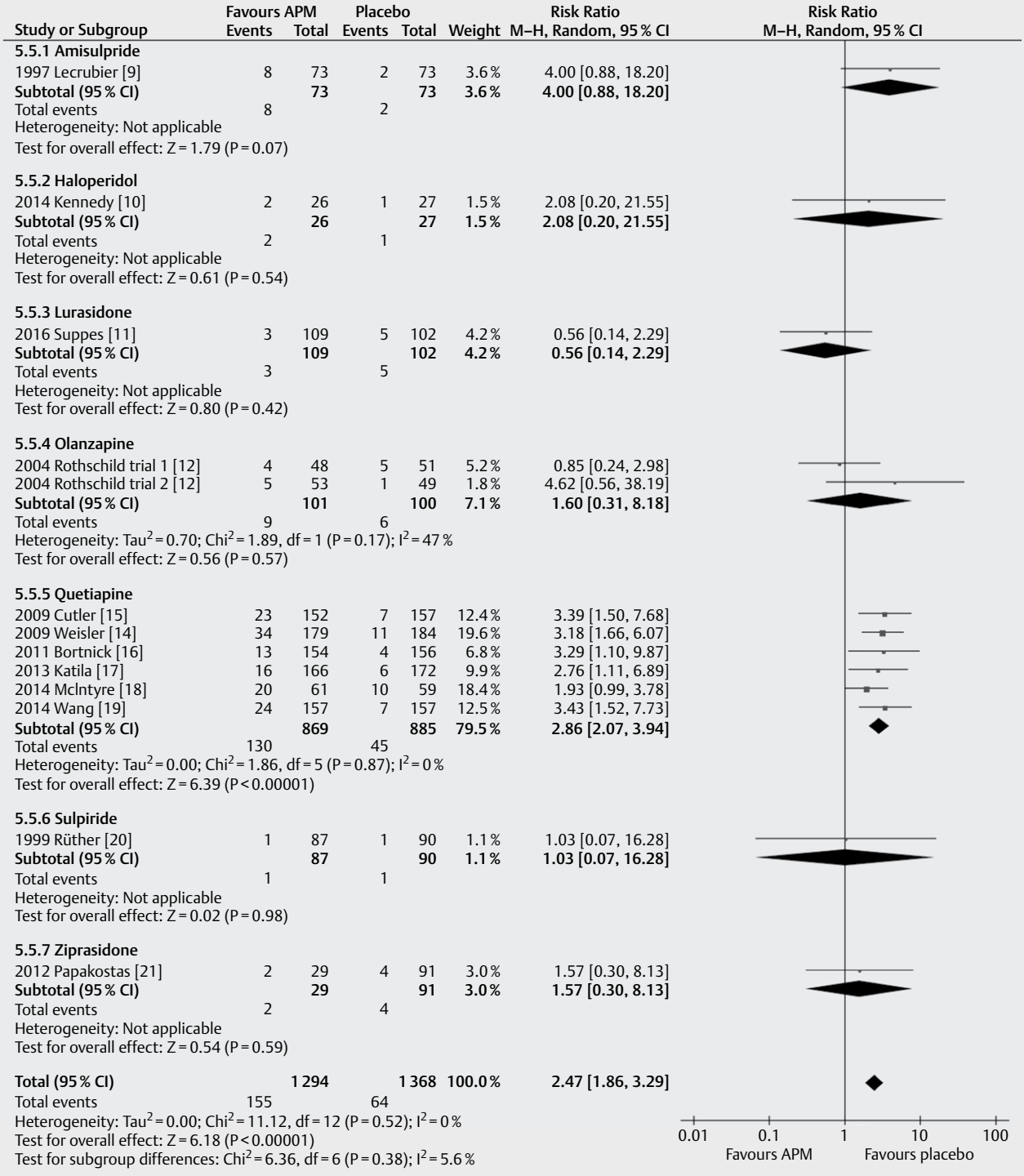
▶ **Fig. 2** Study discontinuation; (**a**) Study discontinuation due to all causes

es in study discontinuation due to adverse events between individual antidepressants and placebo in favor of placebo (odds ratios ranged from 1.64 of vortioxetine to 4.44 of clomipramine) [35]. Also, APM was associated with significantly increased risks of individual adverse events such as EPS, somnolence, and anticholinergic and metabolic side effects. In the subgroup analyses, no clear differences were found in most adverse events such as EPS, somnolence, and metabolic side effects among individual antipsychotics, which may be attributed to reductions in the statistical powers in the subgroup analyses. On the other hand, anticholinergic side effects such as constipation and dry mouth were less frequent for amisulpride and sulpiride, which have little or no anticholinergic



▶ **Fig. 2** Study discontinuation; (**b**) Study discontinuation due to lack of efficacy

effect, than for other antipsychotics. One review reported that quetiapine extended-release significantly increases the risk of the study discontinuation due to adverse events versus placebo in patients with bipolar depression or MDD, but not in those with schizophrenia [44]. Other reviews also indicated that quetiapine is associated with significantly higher risks of EPS and somnolence than placebo in patients with bipolar disorder, particularly in those with bipolar depression, but not in those with schizophrenia [45–47]. These findings are consistent with the results of the current meta-analysis. In terms of metabolic side effects, there was a significant difference in only increased appetite between APM and placebo in favor of placebo, but no significant difference was observed in weight gain. The results may be attributed to the small number of included RCTs conducted for a short duration (i. e., ≤ 12 weeks) because weight gain follows an appetite increase. Nonetheless, clinicians need to closely monitor metabolic side effects in patients treated with APM, given that a recent review determined that APM causes significant weight gain in patients with bipolar disorder compared with placebo, regardless of treatment duration [47]. It should be noted that the present meta-analysis did not evaluate serious adverse events associated with antipsychotics, such as tardive dyskinesia and neuroleptic malignant syndrome, because



▶ **Fig. 2** Study discontinuation; (**c**) Study discontinuation due to adverse events

these relatively rare adverse events were not reported in the included studies. Considering that mood disorders are a risk factor for tardive dyskinesia [48, 49], clinicians should also continue to pay attention to these potentially serious adverse events.

The present study has several limitations. First, although this meta-analysis included several antipsychotics, almost half of the studies examined quetiapine and only one study examined each of the other antipsychotics.Thus, the results may have been largely influenced by studies examining quetiapine. Second, the treatment duration in almost all studies was 12 weeks or shorter; therefore, we could not evaluate the long-term effectiveness, efficacy, and safety of APM for MDD. This is especially relevant for depression in light of the chronic and recurrent nature of the illness. Third, because all patients had moderate-to-severe depression, the findings

▶ **Table 2** Depression severity change.

	Number of studies	Number of APM	Number of Placebo	Difference			Heterogeneity	
				MD or SMD	95 % CI	P	P	I^2 (%)
Primary depression severity scale								
Haloperidol	1	22	26	0.01	−0.56, 0.58	0.97	NA	NA
Lurasidone	1	108	100	−0.73	−1.01, −0.45	<0.001	NA	NA
Olanzapine	2	90	94	−0.25	−0.54, 0.04	0.09	0.40	0
Quetiapine	2	225	230	−0.62	−0.81, −0.43	<0.001	0.94	0
Ziprasidone	1	29	91	−0.24	−0.66, 0.18	0.26	NA	NA
Total	7	474	541	−0.45	−0.64, −0.25	<0.001	0.06	51
CGI-S								
Haloperidol	1	22	26	−0.52	−1.14, 0.10	0.10	NA	NA
Lurasidone	1	108	100	−0.60	−0.88, −0.32	<0.001	NA	NA
Olanzapine	2	92	94	−0.20	−0.79, 0.38	0.49	0.10	64
Quetiapine	2	225	230	−0.71	−1.16, −0.26	0.002	0.02	81
Ziprasidone	1	29	91	0.40	−0.14, 0.94	0.15	NA	NA
Total	7	476	541	−0.41	−0.70, −0.12	0.005	<0.001	75
HDRS-17								
Haloperidol	1	22	26	0.05	−2.91, 3.01	0.97	NA	NA
Quetiapine	2	225	230	−5.63	−8.42, −2.85	<0.001	0.09	65
Ziprasidone	1	29	91	−1.70	−4.72, 1.32	0.27	NA	NA
Total	4	276	347	−3.34	−6.38, −0.29	0.03	0.001	81
MADRS								
Lurasidone	1	108	100	−7.50	−10.27, −4.73	<0.001	NA	NA
Quetiapine	1	164	171	−7.54	−10.16, −4.92	<0.001	NA	NA
Total	2	272	271	−7.52	−9.42, −5.62	<0.001	0.98	0
SDS								
Lurasidone	1	108	100	−4.80	−7.29, −2.31	<0.001	NA	NA
Quetiapine	1	61	59	−1.90	−4.54, 0.74	0.18	NA	NA
Total	2	169	159	−3.38	−6.22, −0.54	0.02	0.12	59
Q-LES-Q-SF								
Quetiapine	2	225	230	6.74	4.03, 9.45	<0.001	0.45	0
Total	2	225	230	6.74	4.03, 9.45	<0.001	0.45	0

Abbreviations: APM, antipsychotic monotherapy; CGI-S, Clinical Global Impression – Severity scale; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MD, mean difference; NA, not applicable; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SDS, Sheehan Disability Scale; SMD, standardized mean difference

of this meta-analysis cannot be applied to mild-to-moderate depression or the most severe or psychotic depression. Fourth, a small number of studies contributed to the meta-analysis of depressive symptom severity assessed using rating scales (i. e., the HDRS and MADRS), which may have resulted in insufficient statistical power, particularly for the sensitivity analyses. Fifth, some of the included studies included patients who had MDD with specific conditions. This heterogeneity of studies may have influenced the results. However, the additional meta-analysis of studies that included MDD without any other conditions confirmed unchanged significant differences in response rates, remission rates, and changes in the primary depression severity scale in favor of APM, and study discontinuation due to adverse events and several individual adverse events in favor of placebo (data not shown). Sixth, adverse events have probably not been systematically assessed in the included studies. Furthermore, in addition to the risk of blinding of outcome assessment, blinding of participants may not have been assured for patients who experienced adverse events more specific to antipsychotics such as EPS, weight gain, and sedation. Seventh, there are risks to over- or under-estimation of the response and remission rates by dividing continuous variables (i. e., scores on rating scales) into the dichotomous variables [50], although in this meta-analysis, significant differences were also found in depression severity scales in favor of APM. Lastly, this meta-analysis included several studies that had a high reporting bias. However, the sensitivity analyses of the studies with a low reporting bias in the additional meta-analysis found similar results (data not shown).

In conclusion, this meta-analysis of 13 RCTs showed the antidepressant effects of APM in the acute phase of MDD. However, clinicians should be aware of the increased risks of some adverse events and carefully consider if APM should be used for patients with MDD. Given that no clear relationship between antipsychotic dose and effectiveness, efficacy, or safety was observed and that patients with mood disorders are sensitive to adverse events, clinicians should use the lowest effective dose of antipsychotics and carefully monitor the occurrence of adverse events. Further studies are

needed to examine the efficacy and safety of second-generation antipsychotics other than quetiapine for MDD and elucidate the mechanism of their antidepressant effects.

Author contribution

Dr. Takeuchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Dr. Takeuchi.
Acquisition, analysis, or interpretation of data, and drafting of the manuscript: Dr. Nishi, Dr. Sawada, and Dr. Takeuchi.
Critical revision of the manuscript for important intellectual content: Dr. Uchida and Dr. Mimura.
Statistical analysis: Dr. Nishi and Dr. Sawada.
Administrative, technical, or material support: Dr. Takeuchi.
Supervision: Dr. Takeuchi.

Data availability

The data that support the findings of this study are available from the corresponding author (H.T.) on reasonable request. The corresponding author had full access to all the data in the study.

Conflict of Interest

Drs. Nishi and Sawada have no conflict of interest to declare. Dr. Uchida has received grants from Eisai, Daiichi Sankyo, Meiji-Seika Pharma, Mochida, Otsuka, and Sumitomo Pharma; speaker's fees from Eisai, Meiji-Seika Pharma, Otsuka, and Sumitomo Pharma; and consulting fees from Sumitomo Pharma. Dr. Mimura has received grants from Daiichi Sankyo, Eisai, Mitsubishi Tanabe Pharma, Pfizer, Shionogi, Takeda, and Tsumura; and speaker's fees from Daiichi Sankyo, Eisai, Eli Lilly, Fujifilm RI Pharma, Janssen, Mochida, MSD, Nippon Chemiphar, Novartis Pharma, Ono, Otsuka, Pfizer, Sumitomo Pharma, Takeda, Tsumura, and Yoshitomiyakuhin. Dr. Takeuchi has received grants from Daiichi Sankyo and Novartis Pharma; speaker's fees from EA Pharma, Kyowa, Janssen, Lundbeck, Meiji Seika Pharma, Otsuka, Sumitomo Pharma, Takeda, and Yoshitomiyakuhin; and consulting fees from Janssen, Mitsubishi Tanabe Pharma, Ono, and Sumitomo Pharma.

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