Single Versus Multiple Daily Dosing Regimens of Psychotropic Drugs for Psychiatric Disorders:
A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To compare efficacy and safety of single daily dosing (Single-DD) vs multiple daily dosing (Multiple-DD) regimens of psychotropic drugs, the authors conducted a systematic review and meta-analysis.

Data Sources: A systematic literature search of MEDLINE and Embase was conducted with keywords related to dosing regimens and psychotropic drugs (last search: December 30, 2019)

Study Selection: Randomized controlled trials comparing clinical outcomes between Single-DD and Multiple-DD of the same formulation of the same psychotropic drugs in patients with psychiatric disorders were included.

Data Extraction: Data on study discontinuation, psychopathology, and treatment-emergent adverse events (TEAEs) were extracted.

Results: A total of 32 studies with 34 paired comparisons involving 3,142 patients met the eligibility criteria and were included in the meta-analysis. Various types of psychotropic drugs were examined: antidepressants (22 comparisons), antipsychotics (7 comparisons), benzodiazepines (2 comparisons), mood stabilizers (2 comparisons), and antidepressant-benzodiazepine combination (1 comparison). There was no significant difference in study discontinuation due to all causes (30 comparisons, N = 2,883, risk ratio [RR] = 1.01, 95% CI = 0.94 to 1.09, *P* = .77), lack of efficacy (22 comparisons, N = 2,307, RR = 1.06, 95% CI = 0.84 to 1.33, *P* = .62), or adverse events (25 comparisons, N = 2,571, RR = 0.93, 95% CI = 0.75 to 1.14, *P* = .47) between the Single-DD and Multiple-DD groups. No significant difference was found in changes in psychopathology (8 comparisons, N = 1,337, standardized mean difference = 0.00, 95% CI = –0.11 to 0.11, *P* = .99) between the 2 groups. These results were also true for any type of psychotropic drugs. In terms of TEAEs, however, there were significant differences in anxiety (4 comparisons, N = 347, RR = 0.53, 95% CI = 0.33 to 0.84, *P* = .007) and sleepiness (3 comparisons, N = 934, RR = 0.82, 95% CI = 0.68 to 0.99, *P* = .04) in favor of the Single-DD group.

Conclusions: The findings suggest Single-DD can be clinically adopted regardless of type of psychotropic drugs in patients with psychiatric disorders in general.

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How the dose of psychotropic drug is fragmented within a day (ie, daily dosing regimen of psychotropic drug) is traditionally determined based on its peripheral elimination half-life. In general, product monographs and package inserts recommend that psychotropic drugs with a < 24-hour half-life are to be administered in a divided dosing regimen (ie, multiple daily dosing [Multiple-DD] regimen) and those with a ≥ 24-hour half-life in a once-daily dosing regimen (ie, single daily dosing [Single-DD] regimen). However, real-world clinical practice indicates that this simple principle is not always followed. For instance, a cross-sectional survey showed that clozapine was prescribed in a once-daily dosing regimen in approximately 75% of patients in the United States and Canada, although the product monograph in both countries states that clozapine should be administered twice or 3 times a day.[1]

Maintaining good adherence to medications is critically important to maximize their therapeutic effects,[2] and a simple drug regimen is advantageous from this viewpoint.[3] The field of psychiatry is no exception; some past randomized controlled trials (RCTs) endeavored to compare efficacy and safety between Single-DD and Multiple-DD of various types of psychotropic drugs including antipsychotics,[4–6] antidepressants,[7–9] benzodiazepines,[10–12] antiepileptics,[13] and lithium.[14] To our knowledge, there have been only 2 meta-analyses that focused on this topic,[15,16] suggesting that Single-DD is not inferior to Multiple-DD in terms of efficacy and acceptability; however, these meta-analyses only included RCTs of antidepressants and were published more than 15 years ago. To address this clinically important question, we conducted a systematic review and meta-analysis of RCTs comparing Single-DD and Multiple-DD of all types of psychotropic drugs for psychiatric disorders.

METHODS

Literature Search and Study Selection

We conducted a systematic literature search in accordance with the Preferred Reporting Items

Clinical Points

- This meta-analysis included 32 randomized controlled trials comparing clinical outcomes between single and multiple daily dosing regimens of the same formulation of the same psychotropic drugs in patients with psychiatric disorders.
- No significant differences were found in study discontinuation or psychopathology between single and multiple daily dosing regimens, while there were significant differences in anxiety and sleepiness in favor of a single daily dosing regimen.
- A single daily dosing regimen can be a viable option regardless of psychotropic types in patients with psychiatric disorders in general.

for Systematic Reviews and Meta-Analyses (PRISMA) statement[17] to identify RCTs comparing Single-DD and Multiple-DD regimens of all types of psychotropic drugs for psychiatric disorders (last search: December 30, 2019). To this end, MEDLINE and Embase were searched with the following keywords: (((once[ti] OR twice[ti] OR thrice[ti]) AND (daily[ti] OR day[ti])) OR ((dosing[ti] OR dose*[ti] OR dosage*[ti]) AND (regimen*[ti] OR schedule*[ti] OR single[ti] OR multiple[ti] OR divided[ti] OR split[ti] OR qd[ti] OR quaque die[ti] OR qhs[ti] OR quaque hora somni[ti] OR bid[ti] OR bis in die[ti] OR tid[ti] OR ter in die[ti]))) AND (psychotropic* OR antipsychotic* OR antidepressant* OR lithium OR divalproex OR valpro* OR lamotrigine OR carbamazepine OR mood stabilizer* OR benzodiazepine* OR antianxi* OR hypnotic*). We also searched CENTRAL using the same keywords to check if we had missed any other literature and conducted a hand search. Two authors (Y.K. and Y.S.) independently selected studies that met the following inclusion criteria: an RCT comparing clinical outcome(s) between Single-DD and Multiple-DD of the same formulation of the same psychotropic drugs(s) in patients with psychiatric disorder(s). Literature reported in languages other than English was excluded. Any disagreements about the study selection were resolved by consensus with 2 authors (Y.K. and Y.S.) under the supervision of the senior author (H.T.).

Two authors (Y.K. and Y.S.) independently assessed risk of bias for the selected studies according to the Cochrane Handbook for Systematic Reviews of Interventions (available at http://handbook.cochrane.org). Any disagreements about the assessment were resolved by consensus with 2 authors (Y.K. and Y.S.) under the supervision of the senior author (H.T.).

Data Extraction

Two authors (Y.K. and Y.S.) independently extracted the following clinical outcome data in both Single-DD and Multiple-DD groups from the selected studies: (1) the number of patients who discontinued the study due to all causes, lack of efficacy, and adverse events; (2) the mean ± SD of changes in scores on primary psychopathology scales from baseline to endpoint; and (3) the number of patients who experienced treatment-emergent adverse events (TEAEs) that were reported in ≥ 3 out of the identified comparisons. Because there were variants in expression of TEAEs, we combined those that were considered a synonymous term. Two studies included 2 Single-DD regimens (ie, at night and in the morning)[18,19]; we used the data in the night group. Also, 1 study included 2 Multiple-DD regimens (ie, twice and 3 times daily dosing)[20]; we used the data in the twice daily dosing group. We employed WebPlotDigitizer (available at https://automeris.io/WebPlotDigitizer/) if the included studies provided only graphs for the data. Any disagreements about the data extraction were resolved by consensus with 2 authors (Y.K. and Y.S.) under the supervision of the senior author (H.T.). If the selected studies provided insufficient data, we contacted the corresponding authors to obtain additional information necessary for the meta-analyses.

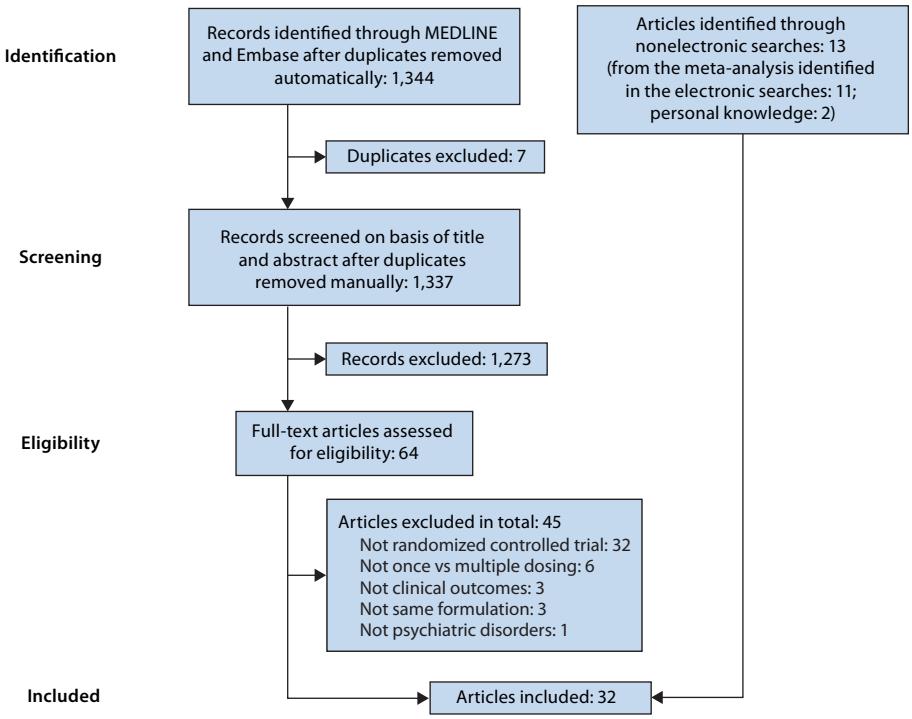
Data Analysis

We performed meta-analyses using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark; 2014). Outcome data were combined and compared between the Single-DD and Multiple-DD groups. For dichotomous and continuous outcomes, pooled estimates of risk ratios (RRs) and standardized mean differences (SMDs), respectively, were calculated with 2-sided 95% confidence intervals (CIs) using a random-effects model. Study heterogeneities were quantified using I^2 statistic with $I^2 \geq 50\%$ indicating significant heterogeneity. All effect sizes with a $P < .05$ were considered significant. Two authors (Y.K. and Y.S.) independently performed the meta-analyses. Any disagreements about the meta-analyses were resolved by consensus with 2 authors (Y.K. and Y.S.) under the supervision of the senior author (H.T.).

As sensitivity analyses, we separately analyzed the following sets of studies: (1a) double-blind studies; (1b) non–double-blind studies; (2a) studies adopting intention-to-treat analysis; (2b) studies adopting modified intention-to-treat analysis; (2c) studies adopting completer analysis; (3a) studies examining psychotropic drugs with peripheral elimination half-life < 24 hours; (3b) studies examining psychotropic drugs with peripheral elimination half-life ≥ 24 hours; (4a) studies examining psychotropic drugs with the description in the product monograph that the drug should be administered once daily (ie, Single-DD); and (4b) studies examining psychotropic drugs without the description in the product monograph that the drug should be administered once daily (ie, Single-DD).

We further repeatedly performed these analyses in studies examining once vs twice or once vs 3 times daily dosing. One study included twice daily and 3 times daily dosing groups[20]; we used the data in the twice daily and 3 times daily dosing groups for the main analyses and the sensitivity analyses for studies examining once vs 3 times daily dosing, respectively.

Figure 1. PRISMA Flow Diagram of the Literature Search



RESULTS

Included Studies

A total of 32 studies published from 1974 to 2015 involving 3,142 patients (N = 1,598 and N = 1,544 for the Single-DD and Multiple-DD groups, respectively) that met our inclusion criteria were identified (Figure 1).[4–14,18–38] Only 7 studies were published after 2000. As 2 studies included 2 separate comparisons, a total of 34 comparisons were included in the meta-analysis. The characteristics of the eligible studies are summarized in Table 1. Among the 32 studies, 23, 1, and 5 were conducted in a double-blind, rater-blind, and open-label fashion, respectively. Various types of psychotropic drugs were examined: antidepressants (22 comparisons), antipsychotics (7 comparisons), benzodiazepines (2 comparisons), mood stabilizers (2 comparisons), and antidepressant-benzodiazepine combination (1 comparison). The Multiple-DD group included 3 types of regimens: twice daily dosing (17 comparisons), 3 times daily dosing (16 comparisons), and 4 times daily dosing (1 comparison). The authors of 5 studies provided additional data.[4,6,8,14,38] The dose was fixed in 19 comparisons (ie, same doses for both groups), while the dose was flexible in 9 comparisons; the mean dose at the endpoint was lower and higher in the Single-DD group than the Multiple-DD group in 8 and 1 comparisons, respectively.

The results of risk of bias assessment are described in Supplementary Figure 1. The risks of random sequence generation and of allocation concealment were unclear in all of the studies. The risk of incomplete outcome data was high in general, because older studies adopted completer analysis.

Study Discontinuation

There was no significant difference in study discontinuation due to all causes (30 comparisons, N = 2,883, RR = 1.01, 95% CI = 0.94 to 1.09, $P = .77$), lack of efficacy (22 comparisons, N = 2,307, RR = 1.06, 95% CI = 0.84 to 1.33, $P = .62$), or adverse events (25 comparisons, N = 2,571, RR = 0.93, 95% CI = 0.75 to 1.14, $P = .47$) between the Single-DD and Multiple-DD groups of all psychotropic drugs (Figure 2). Moreover, no significant difference in any study discontinuation was found between the 2 groups in any subgroup of antidepressants, antipsychotics, benzodiazepines, mood stabilizers, and antidepressant-benzodiazepine combination.

Psychopathology

No significant difference was found in score changes on psychopathology scales (8 comparisons, N = 1,337, SMD = 0.00, 95% CI = −0.11 to 0.11, $P = .99$) between the Single-DD and Multiple-DD groups (Figure 3). There was no significant difference between the 2 groups in any subgroup of antidepressants, antipsychotics, and mood stabilizers, although caution is necessary as data were relatively scarce for psychopathology, because older studies frequently failed to provide standard deviation or standard error.

Table 1. Summary of Randomized Controlled Trials Examining Single vs Multiple Daily Dosing of Psychotropic Drugs

	Study Design										
Study Year and First Author	Blinding	Study Duration	Diagnosis	Psycho-pathology Scale	Analysis Method	In/ Outpatient Status	Drug Name	Peripheral Elimination Half-Life	Single-DD Indication on a Package Insert?	Dosing Type	Drug Before Assignment
1974 Pearce[21]	DB	3 wk[a]	D	HDRS	NA	Outpatient	Dothiepin	< 24 h[39]	Yes in the UK	qd vs tid	Placebo
1975 Mendels[22]	DB	4 wk	D, N	HDRS	CA	Outpatient	Doxepin	< 24 h[39]	Yes in the US	qd vs qid	NA
1976 Snowdon[23]	DB	4 wk	D	HDRS	NA	Inpatient	Amitriptyline	< 24 h[39]	Yes in the US	qd vs tid	Amitriptyline
1977 Frank (30 mg)[24] 1977 Frank (75 mg)[24]	OL	4 wk	D	HDRS	CA	NA	Clomipramine	< 24 h[39]	Yes in the US	qd vs tid	NA
1977 Mendels[25]	DB	4 wk	D	HDRS	CA	Outpatient	Desipramine	< 24 h[39]	Yes in the US	qd vs tid	NA
1978 Montgomery[26]	DB	4 wk	D	HDRS	CA	Mixed	Mianserin	≥ 24 h[39]	Yes in the UK	qd vs tid	None[c]
1978 Schubert[27]	DB	4 wk[a]	D	HDRS	CA	NA	Clomipramine	< 24 h[39]	Yes in the US	qd vs tid	NA
1980 James[12]	NA	3 wk	D	LSAD	NA	NA	Chlordiazepoxide/ amitriptyline combination	< 24 h[39]	Yes in the US	qd vs tid	NA
1980 De Maio[28]	NA	16.5 d for qd, 13.9 d for bid[d]	D	HDRS	CA	Inpatient	Nomifensine	< 24 h[16]	NA	qd vs bid	NA
1980 Weise[29]	DB	6 wk	D	PDS	CA	Outpatient	Amitriptyline	< 24 h[39]	Yes in the US	qd vs tid	NA
1980 Wheatley (bid)[20] 1980 Wheatley (tid)[20]	NA	2 wk	D	LSAD	NA	NA	Trazodone	< 24 h[39]	Yes in the UK	qd vs bid qd vs tid	NA
1981 Sharma[30]	DB	4 wk	D	HDRS	NA	Inpatient[e]	Dothiepin	< 24 h[39]	Yes in the UK	qd vs tid	NA
1981 Watson (night)[18] 1981 Watson (morning)[18]	DB	6 wk[f]	D	HDRS[f]	CA	Outpatient	Zimelidine	< 24 h[16]	Yes[40]	qd vs bid	Placebo
1982 Ban[31]	DB	6 wk	D, N	HDRS	CA	Inpatient	Amoxapine	< 24 h[16]	Yes in the US	qd vs tid	NA
1983 Mungavin[32]	OL	4 wk	D	HDRS	CA	Outpatient	Trazodone	< 24 h[39]	Yes in the UK	qd vs tid	NA
1984 Ansseau[11]	DB	3 wk[a]	GAD	HARS	ITT	Inpatient	Prazepam	< 24 h[39]	Yes in EEA	qd vs tid	Placebo
1984 Brooks[33]	DB	4 wk[a]	D	HDRS	CA	Mixed	Trazodone	< 24 h[39]	Yes in the UK	qd vs tid	Placebo
1984 Wheatley[34]	DB	6 wk	D	HDRS	NA	NA	Trazodone	< 24 h[39]	Yes in the UK	qd vs bid	NA
1985 Doongaji[10]	DB	6 wk[a]	N	HARS	NA	Outpatient	Clobazam	≥ 24 h[39]	Yes in the US	qd vs bid	Placebo
1985 Siddiqui (night)[19] 1985 Siddiqui (morning)[19]	DB	6 wk[a]	D	HDRS	CA	Outpatient	Fluvoxamine	< 24 h[39]	Yes in the US	qd vs bid	Placebo
1988 Davey[35]	DB	6 wk	MDD	HDRS	NA	NA	Trazodone	< 24 h[39]	Yes in the UK	qd vs tid	NA
1995 Newburn[9]	DB	6 wk	MDD	HDRS	CA, ITT	Mixed	Moclobemide	< 24 h[39]	No	qd vs tid	NA
1998 Amsterdam[8]	DB	6 wk	MDD, BD	HDRS	CA, mITT	Outpatient	Venlafaxine	< 24 h[39]	No	qd vs bid	Placebo
1998 Nair[36]	DB	6 wk	SCZ	PANSS	CA	Mixed	Risperidone	< 24 h[39]	Yes in the US	qd vs bid	NA
1998 Voris[7]	NA	4 wk	MDD	HDRS-SR	ITT	Inpatient	Nefazodone	< 24 h[16]	NA	qd vs bid	NA
2001 Agarwal[37]	OL	8 wk	SCZ	PANSS	mITT	Outpatient	Risperidone	< 24 h[39]	Yes in the US	qd vs bid	None (drug naive) /placebo
2003 Chengappa[6]	DB	8 wk[i]	SCZ[j]/SAD	PANSS	ITT	Inpatient	Quetiapine	< 24 h[39]	Yes in the US	qd vs bid	NA
2008 Weisler[13]	DB	Around 11 wk[a]	BD	YMRS	mITT	Outpatient	Carbamazepine extended-release	< 24 h[k]	NA	qd vs bid	NA
2011 Singh[14]	SB	6 wk	BD	BRMRS	ITT	Inpatient	Lithium	≥ 24 h[39]	Yes in the UK	qd vs bid	NA
2014 Takeuchi[38]	DB	Up to 18 mo	SCZ	PANSS	NA	NA	Perphenazine	< 24 h[39]	NA	qd vs bid	NA
2015 Sun[5]	OL	2 wk	SCZ or SAD	BPRS	CA, ITT	Inpatient	Asenapine	≥ 24 h[39]	NA	qd vs bid	NA
2015 Takeuchi (olanzapine)[4]	DB	Up to 18 mo	SCZ	PANSS	mITT	NA	Olanzapine	≥ 24 h[39]	Yes in the US	qd vs bid	NA
2015 Takeuchi (risperidone)[4]							Risperidone	< 24 h[39]	Yes in the US	qd vs bid	NA

[a]Active treatment period. [b]Completers. [c]After at least 1-week no treatment period. [d]Mean duration. [e]At least for first 2 weeks. [f]At 2 weeks for efficacy and side effects. [g]Provided by the author. [h]Episode duration. [i]Crossover design. [j]Except for catatonic subtype. [k]On a package insert. [l]Treatment duration. [m]Across study duration.

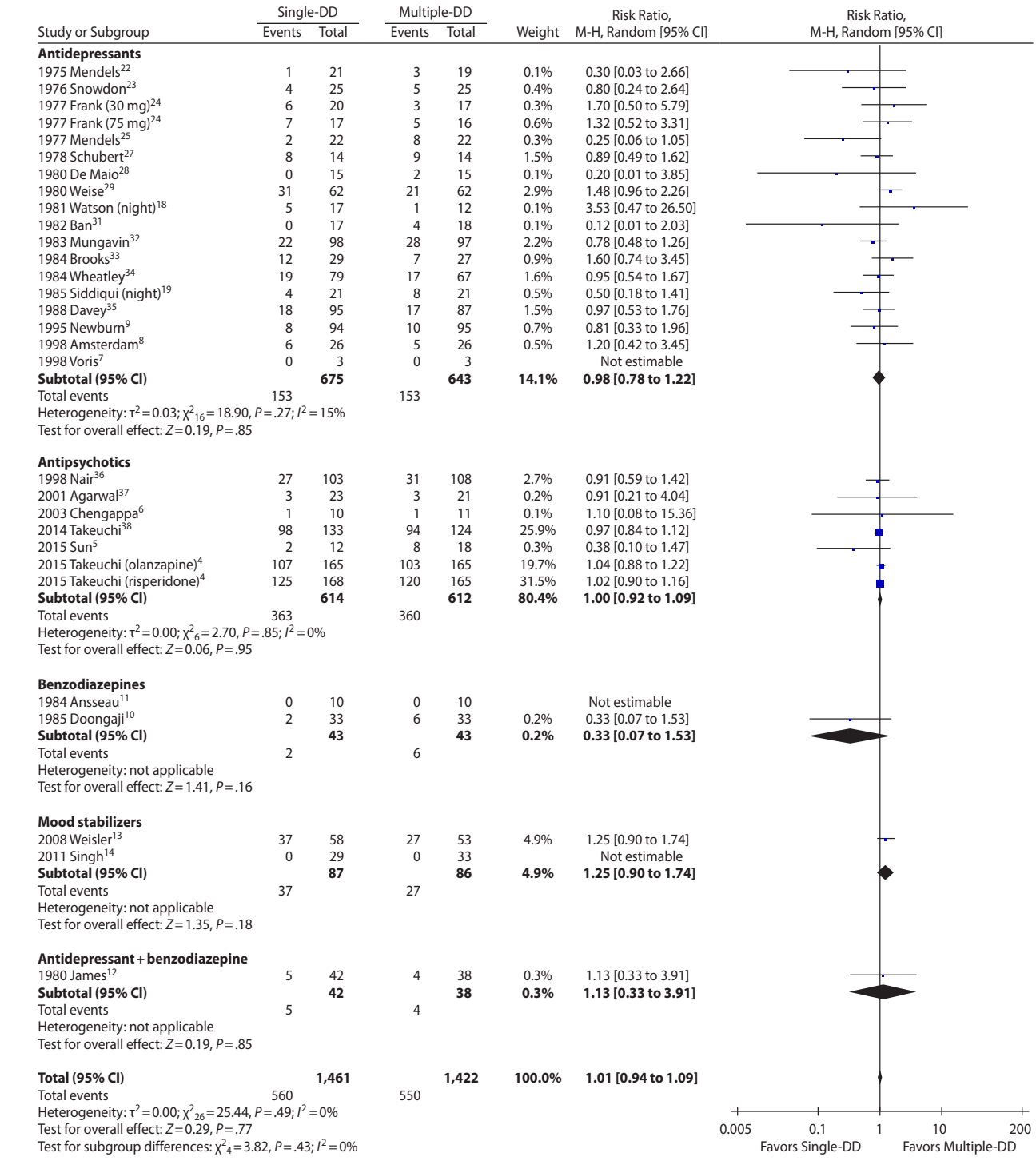
(continued)

Single Daily Dosing						Multiple Daily Dosing					
Total Participants, n	Completers, n	Male, n	Age, Mean, y	Illness Duration, Mean	Dose, Mean, mg/d at the End Point	Total Participants, n	Completers, n	Male, n	Age, Mean, y	Illness Duration, Mean	Dose, Mean, mg/d at the End Point
24[b]	24	8[b]	40[b]	55 wk	225	26[b]	26	7[b]	39[b]	45 wk	225
21	20	5	32.6	34.2 mo	100	19	16	6	33.5	32.5 mo	100
25	21	7[b]	41[b]	NA	150	25	20	7[b]	46[b]	NA	150
20	14	NA	45.0[b]	NA	30	17	14	NA	44.7[b]	NA	30
17	10	NA	39.1[b]	NA	75	16	11	NA	44[b]	NA	75
22	20	6	34.1	NA	150	22	14	6	36.2	NA	150
26[b]	26	NA	NA	NA	60	24[b]	24	NA	NA	NA	60
14	6	1[b]	NA	NA	150	14	5	0[b]	NA	NA	150
42	37[15]	NA	NA	NA	15/37.5	38	34[15]	NA	NA	NA	15/37.5
15	15	15	43.36	NA	178.6	15	13	13[b]	40.0[b]	NA	171.15[b]
62	31	NA	NA	NA	NA	62	41	NA	NA	NA	NA
34	NA	NA	NA	NA	NA (50–200)	33	NA	NA	NA	NA	NA (100–200)
						20	NA	NA	NA	NA	NA (75–200)
14[b]	14	4[b]	46.1[b]	NA	NA (75–150)	14[b]	14	6[b]	40.2[b]	NA	NA (75–150)
17	12	NA	NA	NA	200	12	11	NA	NA	NA	200
10	9	NA	NA	NA	200						
17	17	5	36.5	NA	250 for D, 180 for N	18	14	5	38.8	NA	250 for D, 180 for N
98	76	24	42	NA	200	97	69	30	44	NA	200
10	10	4	46.5	5.0 y	40	10	10	7	42.7	4.7 y	40
29	17	7[b]	46[b]	NA	NA (100–400)	27	20	7[b]	42[b]	NA	NA (100–400)
79	60	23[b]	49.5[b]	NA	130	67	50	13[b]	52[b]	NA	144
33	31	17[c]	28.39[b]	8.77 mo[b]	20	33	27	13[b]	29.74[b]	7.84 mo[b]	20
21	17	9	38	NA	100	21	13	8	40	NA	100
20	10	4	45	NA	100						
95	77	NA	NA	NA	150	87	70	NA	NA	NA	150
94	86	46	43.5	NA	533	95	85	52	42.8	NA	550
26[g]	20[g]	9 (n = 25)	43.0 (n = 25)	90 wk (n = 25)[h]	NA (150/225)	26[g]	21[g]	8 (n = 23)	42.0 (n = 23)	128 wk (n = 23)[h]	NA (150/225)
103	76	69	33.0	NA	8	108	77	73	34.0	NA	8
3	3	3	63.0	NA	467	3	3	3	46.0	NA	467
23	20	14	34[b]	5[b]	5[b]	21	18	13	37[b]	5.9[b]	5.3[b]
10	9	NA	NA	NA	NA (400/600)	11	10	NA	NA	NA	NA (400/600)
58	21	19	37.1	NA	656.4	53	26	23	36.9	NA	727.3
29	29	29	29.2	NA	1,075.9	33	33	33	27.7	NA	1213.6
133	35	97	40.8	16.4 y[l]	19.6 (n = 124)[m]	124	30	99	39.1	14.6 y[l]	21.8 (n = 117)[m]
12	10	NA	NA	NA	10	18	10	NA	NA	NA	10
169	58	119	39.8	16.7 y[l]	18.8 (n = 153)[m]	167	62	125	41.9	16.3 y[l]	21 (n = 156)[m]
173	43	125	40.0	16.5 y[l]	3.75 (n = 149)[m]	168	45	128	41.3	17.3 y[l]	4.04 (n = 155)[m]

Abbreviations: BAD = bipolar affective disorder, BD = bipolar disorder, bid = twice a day, BPRS = Brief Psychiatry Rating Scale, BRMRS = Bech-Rafaelsen Mania Rating Scale, CA = completer analysis, D = depression, DB = double-blind, DN = drug naive, EEA = European Economic Area, GAD = generalized anxiety disorder, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, HDRS-SR = Hamilton Depression Rating Scale—Self Report version, ITT = intention-to-treat, LSAD = Leeds Scale for the Self-Assessment of Anxiety and Depression, MDD = major depressive disorder, mITT = modified intention-to-treat, N = neurosis, NA = not available, OL = open-label, PANSS = Positive and Negative Syndrome Scale, PDS = Physician Depression Scale, qd = once a day, qid = 4 times a day, SAD = schizoaffective disorder, SB = single-blind, SCZ = schizophrenia, Single-DD = single daily dosing, tid = 3 times a day, YMRS = Young Mania Rating Scale.

Figure 2. Study Discontinuation

A. Study Discontinuation Due to All Causes



(continued)

Treatment-Emergent Adverse Events

A total of 35 types of TEAEs were included in the meta-analysis. There were significant differences between the Single-DD and Multiple-DD groups in anxiety (4 comparisons, N = 347, RR = 0.53, 95% CI = 0.33 to 0.84, $P = .007$) and sleepiness (3 comparisons, N = 934, RR = 0.82, 95% CI = 0.68 to 0.99, $P = .04$), both in favor of the Single-DD group (Figure 4). The same results were found in the subgroup of antipsychotics.

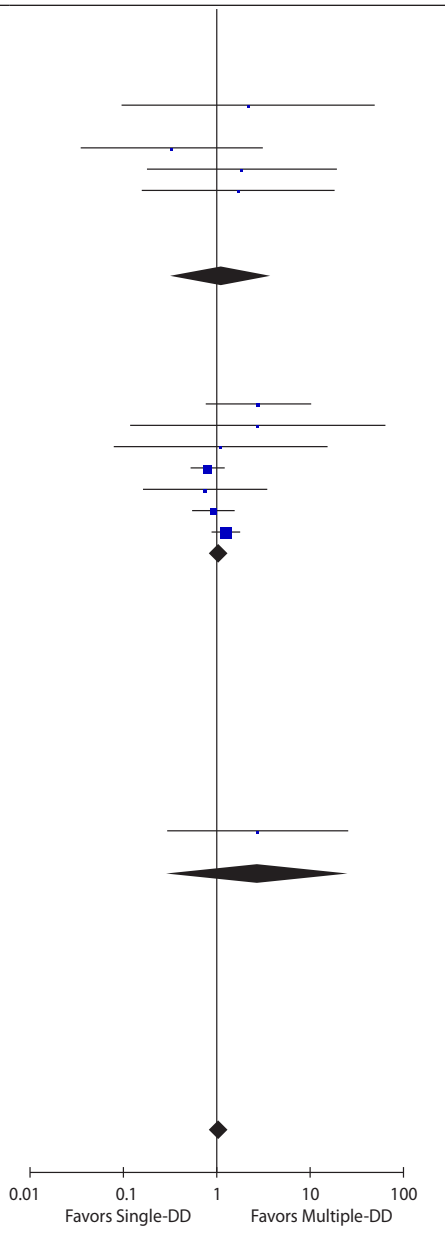
Sensitivity Analyses

While there were no significant differences in any study discontinuation or psychopathology between the Single-DD and Multiple-DD groups in any sensitivity analyses

Figure 2 (continued).

B. Study Discontinuation Due to Lack of Efficacy

Study or Subgroup	Single-DD Events	Single-DD Total	Multiple-DD Events	Multiple-DD Total	Weight	Risk Ratio, M-H, Random [95% CI]
Antidepressants						
1977 Frank (30 mg)[24]	0	20	0	17		Not estimable
1977 Frank (75 mg)[24]	0	17	0	16		Not estimable
1980 De Maio[28]	0	15	0	15		Not estimable
1981 Watson (night)[18]	1	17	0	12	0.5%	2.17 [0.10 to 49.07]
1982 Ban[31]	0	17	0	18		Not estimable
1983 Mungavin[32]	1	98	3	97	1.0%	0.33 [0.03 to 3.12]
1984 Brooks[33]	2	29	1	27	0.9%	1.86 [0.18 to 19.38]
1984 Wheatley[34]	2	79	1	67	0.9%	1.70 [0.16 to 18.30]
1995 Newburn[9]	0	94	0	95		Not estimable
1998 Amsterdam[8]	0	26	0	26		Not estimable
1998 Voris[7]	0	3	0	3		Not estimable
Subtotal (95% CI)		**415**		**393**	**3.4%**	**1.11 [0.32 to 3.79]**
Total events	6		5			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 1.61$, $P = .66$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.16$, $P = .87$						
Antipsychotics						
1998 Nair[36]	8	103	3	108	3.1%	2.80 [0.76 to 10.25]
2001 Agarwal[37]	1	23	0	21	0.5%	2.75 [0.12 to 64.04]
2003 Chengappa[6]	1	10	1	11	0.7%	1.10 [0.08 to 15.36]
2014 Takeuchi[38]	30	133	35	124	29.0%	0.80 [0.52 to 1.22]
2015 Sun[5]	2	12	4	18	2.2%	0.75 [0.16 to 3.47]
2015 Takeuchi (olanzapine)[4]	23	165	25	165	18.8%	0.92 [0.55 to 1.55]
2015 Takeuchi (risperidone)[4]	51	168	40	165	41.2%	1.25 [0.88 to 1.78]
Subtotal (95% CI)		**614**		**612**	**95.6%**	**1.05 [0.83 to 1.32]**
Total events	116		108			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 5.54$, $P = .48$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.38$, $P = .70$						
Benzodiazepines						
1984 Ansseau[11]	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events	0		0			
Heterogeneity: not applicable						
Test for overall effect: not applicable						
Mood stabilizers						
2008 Weisler[13]	3	58	1	53	1.0%	2.74 [0.29 to 25.55]
2011 Singh[14]	0	29	0	33		Not estimable
Subtotal (95% CI)		**87**		**86**	**1.0%**	**2.74 [0.29 to 25.55]**
Total events						
Heterogeneity: not applicable						
Test for overall effect: $Z = 0.89$, $P = .38$						
Antidepressant + benzodiazepine						
1980 James[12]	0	42	0	38		Not estimable
Subtotal (95% CI)		**42**		**38**		**Not estimable**
Total events	0		0			
Heterogeneity: not applicable						
Test for overall effect: not applicable						
Total (95% CI)		**1,168**		**1,139**	**100.0%**	**1.06 [0.84 to 1.33]**
Total events	125		114			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{11} = 7.87$, $P = .73$; $I^2 = 0\%$						
Test for overall effect: $Z = 0.49$, $P = .62$						
Test for subgroup differences: $\chi^2_2 = 0.71$, $P = .70$; $I^2 = 0\%$						



(continued)

(Supplementary Table 1), some significant differences in TEAEs were found between the 2 groups in some sensitivity analyses (Supplementary Table 2). Overall, anxiety and sleepiness were favorable in the Single-DD group, while a couple of items including dizziness and drowsiness were in favor of the Multiple-DD group in some sensitivity analyses.

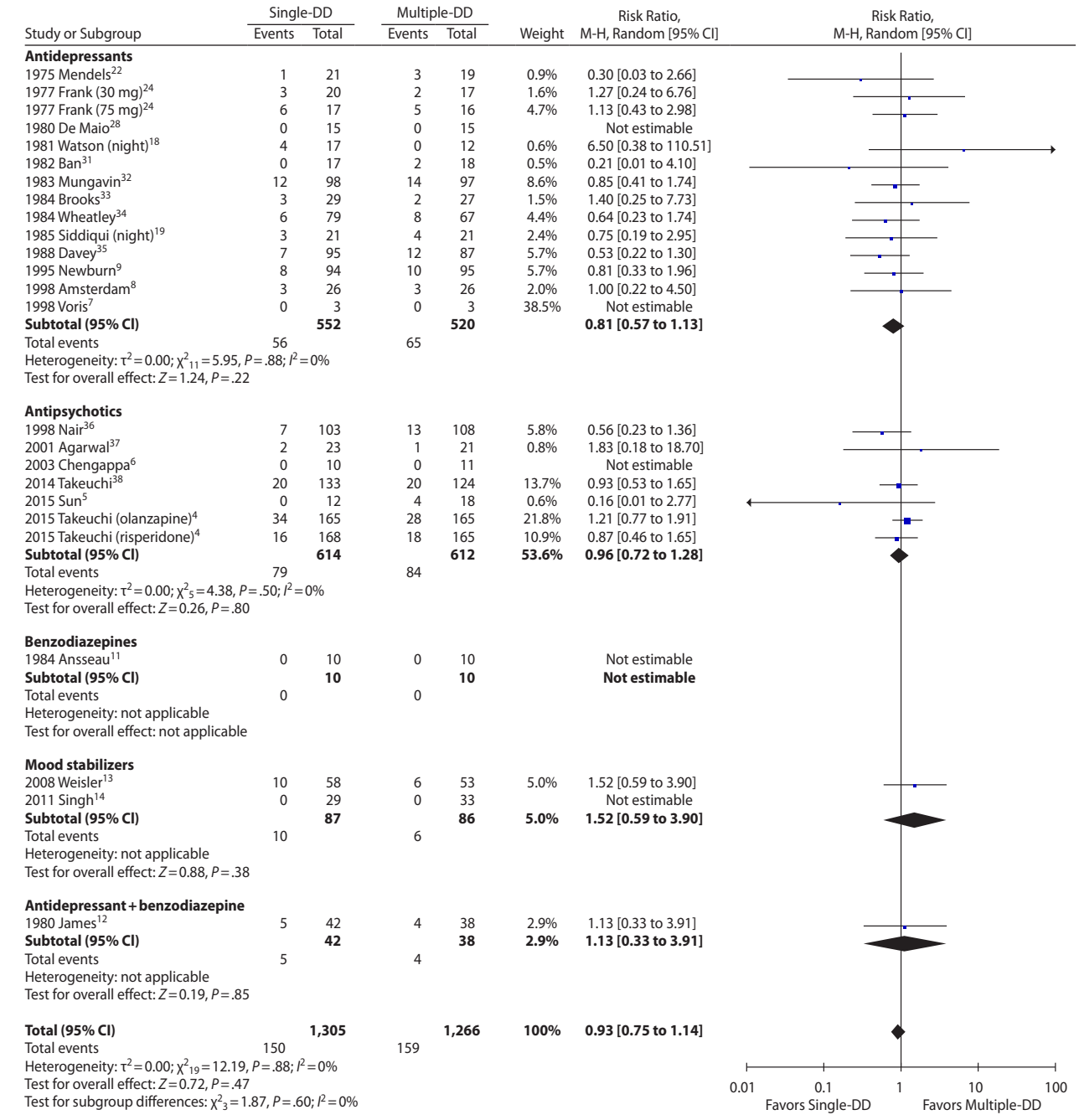
DISCUSSION

The current meta-analysis revealed no significant differences in all-cause study discontinuation, discontinuation due to lack of efficacy as well as adverse events, or changes in psychopathology between Single-DD and Multiple-DD regimens of both all and individual types of psychotropic drugs. In terms of TEAEs, however, there were significant differences in anxiety and sleepiness in favor of Single-DD regimen. The findings corroborate the previous meta-analyses focusing on antidepressants,[15,16] but the advantage of our meta-analysis is that all types of psychotropic drugs were included.

Although dosing interval of a psychotropic drug is generally determined according to its peripheral elimination half-life, our meta-analysis found no superiority for Multiple-DD over Single-DD, regardless of the half-lives

Figure 2 (continued).

C. Study Discontinuation Due to Adverse Events

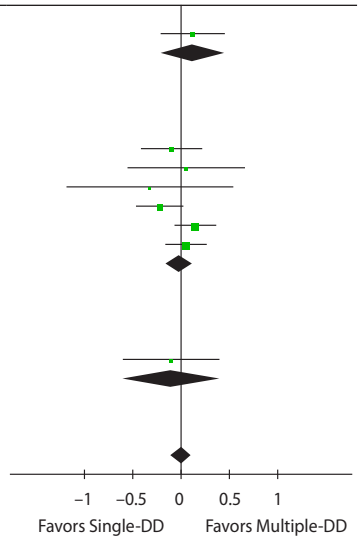


Abbreviations: M-H = Mantel-Haenszel, Multiple-DD = multiple daily dosing, Single-DD = single daily dosing.

of the compounds. The dosing frequency is associated with medication adherence and is reasonably a topic of scrutiny; a systematic review showed that less frequent dosing is plausibly related to better medication adherence in chronic psychiatric diseases.[41] In addition, a meta-analysis found that patients receiving Single-DD were more adherent than those receiving Multiple-DD in chronic diseases,[42] and another meta-analysis of 4 RCTs indicated that Single-DD was associated with a lower risk of nonadherence than Multiple-DD in chronic cardiovascular disease.[43] Although Single-DD may facilitate adherence to psychotropic drugs, thereby improving long-term outcomes in chronic conditions, the current meta-analysis was not able to address this clinically important question. In the current meta-analysis, only 6 included RCTs measured medication adherence as a clinical outcome[4,6,13,29,35,38]; 5 studies reported no significant difference between the Single-DD and Multiple-DD groups, and 1 study found superiority in

Figure 3. Psychopathology

Study or Subgroup	Single-DD Mean	Single-DD SD	Single-DD Total	Multiple-DD Mean	Multiple-DD SD	Multiple-DD Total	Weight	Standard Mean Difference, IV, Random [95% CI]
Antidepressants								
1983 Mungavin[32]	−15.9	4.1	73	−16.4	4.1	67	10.5%	0.12 [−0.21 to 0.45]
Subtotal (95% CI)			**73**			**67**	**10.5%**	**0.12 [−0.21 to 0.45]**
Heterogeneity: not applicable								
Test for overall effect: $Z = 0.72$, $P = .47$								
Antipsychotics								
1998 Nair[36]	−31.5	27	76	−29	23.7	77	11.5%	−0.10 [−0.42 to 0.22]
2001 Agarwal[37]	−31.6	15.3	23	−32.5	17.4	19	3.1%	0.05 [−0.55 to 0.66]
2003 Chengappa[6]	−11	7.2	10	−7.7	11.7	11	1.5%	−0.32 [−1.19 to 0.54]
2014 Takeuchi[38]	−6.2	16.4	133	−2.8	14.1	123	19.1%	−0.22 [−0.47 to 0.02]
2015 Takeuchi (olanzapine)[4]	−6.8	14.9	165	−9.1	16.1	165	24.7%	0.15 [−0.07 to 0.36]
2015 Takeuchi (risperidone)[4]	−3.5	17.3	168	−4.4	17.2	165	25.0%	0.05 [−0.16 to 0.27]
Subtotal (95% CI)			**575**			**560**	**84.9%**	**−0.01 [−0.15 to 0.12]**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 6.04$, $P = 0.30$; $I^2 = 17\%$								
Test for overall effect: $Z = 0.22$, $P = 0.83$								
Mood stabilizers								
2011 Singh[14]	−27.1	16.3	29	−26.5	5.3	33	4.6%	−0.10 [−0.60 to 0.40]
Subtotal (95% CI)			**29**			**33**	**4.6%**	**−0.10 [−0.60 to 0.40]**
Heterogeneity: not applicable								
Test for overall effect: $Z = 0.40$, $P = .69$								
Total (95% CI)	**677**					**660**	**100.0%**	**0.00 [−0.11 to 0.11]**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_7 = 6.74$, $P = .46$; $I^2 = 0\%$								
Test for overall effect: $Z = 0.02$, $P = .99$								
Test for subgroup differences: $\chi^2_2 = 0.72$, $P = .70$; $I^2 = 0\%$								

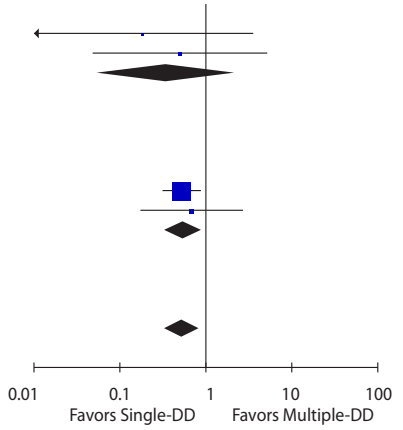


Abbreviations: IV = inverse variance, M-H = Mantel-Haenszel, Multiple-DD = multiple daily dosing, Single-DD = single daily dosing.

Figure 4. Treatment-Emergent Adverse Events With Significant Difference

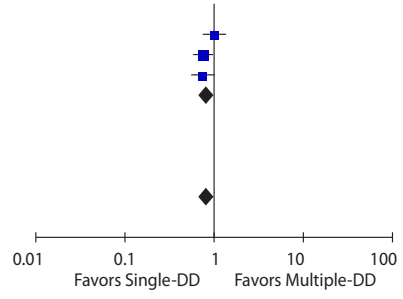
A. Anxiety

Study or Subgroup	Single-DD Events	Single-DD Total	Multiple-DD Events	Multiple-DD Total	Weight	Risk Ratio, M-H, Random [95% CI]
Antidepressants						
1985 Siddiqui (night)[19]	0	21	2	19	2.5%	0.18 [0.01 to 3.56]
1998 Amsterdam[8]	1	26	2	26	4.0%	0.50 [0.05 to 5.18]
Subtotal (95% CI)		**47**		**45**	**6.5%**	**0.34 [0.05 to 2.14]**
Total events	1		4			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.28$, $P = .60$; $I^2 = 0\%$						
Test for overall effect: $Z = 1.15$, $P = .25$						
Antipsychotics						
1998 Nair[36]	17	103	34	108	82.0%	0.52 [0.31 to 0.88]
2001 Agarwal[37]		23	4	21	11.5%	0.68 [0.17 to 2.71]
Subtotal (95% CI)		**126**		**129**	**93.5%**	**0.54 [0.33 to 0.88]**
Total events	20		38			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.13$, $P = 0.72$; $I^2 = 0\%$						
Test for overall effect: $Z = 2.49$, $P = .01$						
Total (95% CI)		**173**		**174**	**100.0%**	**0.53 [0.33 to 0.84]**
Total events	21		42			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 0.64$, $P = .89$; $I^2 = 0\%$						
Test for overall effect: $Z = 2.70$, $P = .007$						
Test for subgroup differences: $\chi^2_1 = 0.23$, $P = .63$; $I^2 = 0\%$						



B. Sleepiness

Study or Subgroup	Single-DD Events	Single-DD Total	Multiple-DD Events	Multiple-DD Total	Weight	Risk Ratio, M-H, Random [95% CI]
Antipsychotics						
2014 Takeuchi[38]	53	133	49	124	30.4%	1.01 [0.75 to 1.36]
2015 Takeuchi (olanzapine)[4]	61	169	80	167	39.2%	0.75 [0.58 to 0.97]
2015 Takeuchi (risperidone)[4]	50	173	65	168	30.4%	0.75 [0.55 to 1.01]
Subtotal (95% CI)		**475**		**459**	**100.0%**	**0.82 [0.68 to 0.99]**
Total events	164		194			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_2 = 2.60$, $P = .27$; $I^2 = 23\%$						
Test for overall effect: $Z = 2.06$, $P = .04$						
Total (95% CI)		**475**		**459**	**100.0%**	**0.82 [0.68 to 0.99]**
Total events	164		194			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_2 = 2.60$, $P = .27$; $I^2 = 23\%$						
Test for overall effect: $Z = 2.06$, $P = .04$						
Test for subgroup differences: not applicable						



Abbreviations: M-H = Mantel-Haenszel, Multiple-DD = multiple daily dosing, Single-DD = single daily dosing.

the Single-DD group. Nevertheless, because these 6 studies did not provide sufficient data, we were not able to perform a meta-analysis. Moreover, medication adherence was variably assessed. Further RCTs are urgently needed to examine the effects of Multiple-DD vs Single-DD of psychotropic drugs on medication adherence as well as on long-term clinical consequences including psychopathology, functioning, and subjective well-being.

The finding of no difference in efficacy between Single-DD and Multiple-DD of psychotropic drugs may be supported by neuroimaging studies. In terms of antipsychotics, for instance, a recent systematic review of studies using positron emission tomography (PET) or single-photon emission computed tomography indicated that pharmacokinetic attenuation of antipsychotics was generally slower at the central level than the peripheral level.[44] As for antidepressants, 2 studies using PET reported that duloxetine, escitalopram, and sertraline showed a sustained time-course of serotonin transporter occupancy compared to the plasma concentrations.[45,46] Given that the PET studies have been consistent in showing that pharmacokinetics of at least some psychotropic drugs are substantially slower centrally than peripherally, drugs that affect the central nervous system may be administered once daily irrespective of the peripheral elimination half-life of the compound. Nonetheless, further investigations are necessary on this issue, and due caution is necessary because there are no neuroimaging studies examining other psychotropic drugs such as benzodiazepines on this topic, possibly due to a lack of good tracers.

Contrary to the findings on efficacy, the current meta-analysis indicated that Single-DD of psychotropic drugs was found to be superior to Multiple-DD in terms of anxiety and sleepiness. It is not clear why Single-DD was associated with less anxiety, although 1 included study speculated that higher peak plasma drug concentrations in Single-DD than Multiple-DD contributed to a greater degree of amelioration of anxiety.[36] The superiority of Single-DD for sleepiness may be due to a more sedative effect during daytime in Multiple-DD. Indeed, 1 study reported that oral risperidone caused sedation more frequently a few hours after administration than at 24 hours,[47] and another study reported that intramuscular olanzapine caused more sedation 2 hours after administration than at 24 hours.[48] If a patient is taking psychotropic drug(s) in Multiple-DD and is suffering from sleepiness and/or anxiety, switching to Single-DD would be a reasonable treatment strategy.

There are several limitations to be noted. First, the data on psychopathology and individual TEAEs were available for only 8 and up to 5 comparisons, respectively, which may have resulted in insufficient statistical power. Second, the current meta-analysis was associated with a high attrition bias, because the vast majority of the included studies were conducted in 1970s and 1980s, adopted the completer analysis method, and were associated with a high attrition rate; half of the studies were judged to have a high risk for incomplete outcome data. As 1970s and 1980s studies included in the meta-analysis examined relatively older antidepressants and benzodiazepines, the findings may not be generalizable to more recent psychotropic agents that are currently more widely utilized. Third, our meta-analysis did not cover all types of psychotropic drugs or psychiatric disorders; for example, no RCTs examining psychostimulants or antidementia drugs were found through our systematic literature search. Fourth, approximately two thirds of the studies did not provide such information, and we were unable to know if these studies examined efficacy of initiating a new drug in Single-DD vs Multiple-DD, switching Multiple-DD to Single-DD for an ongoing drug vs continuing Multiple-DD, or switching Single-DD to Multiple-DD for an ongoing drug vs continuing Single-DD. Fifth, the information on concomitant drugs that could have influenced the results was not sufficiently provided: no concomitant drugs (1 comparison), no psychotropic concomitant drugs (2 comparisons), benzodiazepines and antiparkinsonians allowed (13 comparisons), any drugs allowed (4 comparisons), and no information (14 comparisons). Sixth, no studies reported factors that could affect drug metabolism, such as smoking and metabolizer status. Finally, as previously stated, actual medication adherence has rarely been addressed, and long-term clinical consequences of Single-DD vs Multiple-DD are largely unknown. Further RCTs with various types of psychotropic drugs for diverse psychiatric disorders are needed to confirm the present findings.

In conclusion, the current meta-analysis showed no difference in effectiveness or efficacy between Single-DD and Multiple-DD regimens of psychotropic drugs, regardless of the type of drugs, in patients with psychiatric disorders. Nonetheless, given the superiority of Single-DD over Multiple-DD for tolerability and given its simplicity, Single-DD warrants serious clinical consideration, in particular for patients who suffer anxiety and/or sleepiness or are at risk of suboptimal medication adherence.

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Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Takeuchi H, Powell V, Geisler S, et al. Clozapine administration in clinical practice: once-daily versus divided dosing. *Acta Psychiatr Scand*. 2016;134(3):234–240.
2. Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry*. 2013;12(3):216–226.
3. Ryan R, Santesso N, Lowe D, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. *Cochrane Database Syst Rev*. 2014;(4):CD007768.
4. Takeuchi H, Fervaha G, Lee J, et al. Effectiveness of different dosing regimens of risperidone and olanzapine in schizophrenia. *Eur Neuropsychopharmacol*. 2015;25(3):295–302.
5. Sun X, Hamer R, McEvoy J. Asenapine once daily versus twice daily: impact on patient acceptance in a randomized, open-label, 14-day clinical trial. *J Clin Psychiatry*. 2015;76(7):992–993.
6. Chengappa KN, Parepally H, Brar JS, et al. A random-assignment, double-blind, clinical trial of once- vs twice-daily administration of quetiapine fumarate in patients with schizophrenia or schizoaffective disorder: a pilot study. *Can J Psychiatry*. 2003;48(3):187–194.
7. Voris JC, Shaurette GN, Sebastian PS, et al. Nefazodone: single versus twice daily dose. *Pharmacotherapy*. 1998;18(2):379–380.
8. Amsterdam JD, Hooper MB, Amchin J. Once- versus twice-daily venlafaxine therapy in major depression: a randomized, double-blind study. *J Clin Psychiatry*. 1998;59(5):236–240.
9. Newburn G, Edwards R, Thomas H, et al. A comparison of the efficacy and tolerability of moclobemide given as a single daily dose or in three divided doses per day for the treatment of patients with a major depressive episode (*DSM-III-R*). *J Clin Psychopharmacol*. 1995;15(suppl 2):10S–15S.
10. Doongaji DR, Sheth AS, Apte JS, et al. A comparative study of single and multiple doses of clobazam vs diazepam in anxiety neurosis. *Current Therapeutic Research*. 1985;37(3):398–405.
11. Ansseau M, Doumont A, von Frenckell R, et al. Duration of benzodiazepine clinical activity: lack of direct relationship with plasma half-life: a comparison of single vs divided dosage schedules of prazepam. *Psychopharmacology (Berl)*. 1984;84(3):293–298.
12. James RT, Dean BC. A comparison of a single night-time and a divided daily dosage regimen of a chlordiazepoxide/amitriptyline combination. *Curr Med Res Opin*. 1980;6(8):573–575.
13. Weisler RH, Kalali AH, Cutler AJ, et al. Efficacy and safety of once- versus twice-daily carbamazepine extended-release capsules for the treatment of manic symptoms in patients with bipolar I disorder. *Psychiatry (Edgmont)*. 2008;5(3):35–48.
14. Singh LK, Nizamie SH, Akhtar S, et al. Improving tolerability of lithium with a once-daily dosing schedule. *Am J Ther*. 2011;18(4):288–291.
15. Yildiz A, Pauler DK, Sachs GS. Rates of study completion with single versus split daily dosing of antidepressants: a meta-analysis. *J Affect Disord*. 2004;78(2):157–162.
16. Yýldýz A, Sachs GS. Administration of antidepressants: single versus split dosing: a meta-analysis. *J Affect Disord*. 2001;66(2–3):199–206.
17. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339(7716):b2535.
18. Watson JM, Tiplady B. Zimelidine: comparison of different dosage regimes in general practice. *Acta Psychiatr Scand suppl*. 1981;290:464–470.
19. Siddiqui UA, Chakravarti SK, Jesinger DK. The tolerance and antidepressive activity of fluvoxamine as a single dose compared to a twice daily dose. *Curr Med Res Opin*. 1985;9(10):681–690.
20. Wheatley D. Trazodone in depression. *Int Pharmacopsychiatry*. 1980;15(4):240–246.
21. Pearce JB, Rees WL. A double-blind comparison of three times daily and single night dosage of the tricyclic anti-depressant dothiepin. *J Int Med Res*. 1974;2(1):12–19.
22. Mendels J, Schless A. A controlled comparison of doxepin h.s. and doxepin q.i.d. *J Clin Pharmacol*. 1975;15(7):534–539.
23. Snowdon JA. Double-blind comparison of 3-times daily and single night dosage of amitriptyline, with special reference to side-effects. *Curr Med Res Opin*. 1976;4(6):381–387.
24. Frank P. Comparisons of various clomipramine (Anafranil) dosage regimes. *J Int Med Res*. 1977;5(1 suppl):11–15.
25. Mendels J, Schless AP. Antidepressant effects of desipramine adminstered in two dosage schedules. *Dis Nerv Syst*. 1977;38(4):249–251.
26. Montgomery S, McAuley R, Montgomery DB. Relationship between mianserin plasma levels and antidepressant effect in a double-blind trial comparing a single night-time and divided daily dose regimens. *Br J Clin Pharmacol*. 1978;5(suppl 1):71S–76S.
27. Schubert DS, Miller SI. Are divided doses of tricyclic antidepressants necessary? *J Nerv Ment Dis*. 1978;166(12):875–877.
28. De Maio D, Sesso M, Levi Minzi A, et al. Evaluation of the clinical efficacy of single daily doses of antidepressants. *Prog Neuropsychopharmacol*. 1980;4(6):607–612.
29. Weise CC, Stein MK, Pereira-Ogan J, et al. Amitriptyline once daily vs three times daily in depressed outpatients. *Arch Gen Psychiatry*. 1980;37(5):555–560.
30. Sharma SD. A comparison of a divided and a single dose regime of dothiepin and its therapeutic efficacy. *Indian J Psychiatry*. 1981;23(4):355–359.
31. Ban TA, Fujimori M, Petrie WM, et al. Systematic studies with amoxapine, a new antidepressant. *Int Pharmacopsychiatry*. 1982;17(1):18–27.
32. Mungavin JM, Ankier SI. Comparison of two dosage regimens of trazodone in the treatment of depression. *Clin Trials J*. 1983;20(4):181–188.
33. Brooks D, Prothero W, Bouras N, et al. Trazodone: a comparison of single night-time and divided daily dosage regimens. *Psychopharmacology (Berl)*. 1984;84(1):1–4.
34. Wheatley D. Trazodone: alternative dose regimens and sleep. *Pharmatherapeutica*. 1984;3(9):607–612.
35. Davey A. A comparison of two oral dosage regimens of 150 mg trazodone in the treatment of depression in general practice. *Psychopharmacology (Berl)*. 1988;95(suppl):S25–S30.
36. Nair NP; The Risperidone Study Group. Therapeutic equivalence of risperidone given once daily and twice daily in patients with schizophrenia. *J Clin Psychopharmacol*. 1998;18(2):103–110.
37. Agarwal V, Chadda RK. Once daily risperidone in treatment of schizophrenia. *Indian J Psychiatry*. 2001;43(1):32–35.
38. Takeuchi H, Fervaha G, Uchida H, et al. Impact of once- versus twice-daily perphenazine dosing on clinical outcomes: an analysis of the CATIE data. *J Clin Psychiatry*. 2014;75(5):506–511.
39. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51(1–02):9–62.
40. Heel RC, Morley PA, Brogden RN, et al. Zimelidine: a review of its pharmacological properties and therapeutic efficacy in depressive illness. *Drugs*. 1982;24(3):169–206.
41. Medic G, Higashi K, Littlewood KJ, et al. Dosing frequency and adherence in chronic psychiatric disease: systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. 2013;9:119–131.
42. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm*. 2012;18(7):527–539.
43. Caldeira D, Vaz-Carneiro A, Costa J. The impact of dosing frequency on medication adherence in chronic cardiovascular disease: systematic review and meta-analysis. *Rev Port Cardiol*. 2014;33(7–8):431–437.
44. Kurose S, Mimura Y, Uchida H, et al. Dissociation in pharmacokinetic attenuation between central dopamine D_2 receptor occupancy and peripheral blood concentration of antipsychotics: a systematic review. *J Clin Psychiatry*. 2020;81(5):19r13113.
45. Arakawa R, Tateno A, Kim W, et al. Time-course of serotonin transporter occupancy by single dose of three SSRIs in human brain: a positron emission tomography study with [(11)C]DASB. *Psychiatry Res Neuroimaging*. 2016;251:1–6.
46. Takano A, Suzuki K, Kosaka J, et al. A dose-finding study of duloxetine based on serotonin transporter occupancy. *Psychopharmacology (Berl)*. 2006;185(3):395–399.
47. Chung YC, Park TW, Yang JC, et al. Cognitive effects of a single dose of atypical antipsychotics in healthy volunteers compared with placebo or haloperidol. *J Clin Psychopharmacol*. 2012;32(6):778–786.
48. Kittipeerachon M, Chaichan W. Intramuscular olanzapine versus intramuscular aripiprazole for the treatment of agitation in patients with schizophrenia: a pragmatic double-blind randomized trial. *Schizophr Res*. 2016;176(2–3):231–238.

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Supplementary Material

Article Title: Single Versus Multiple Daily Dosing Regimens of Psychotropic Drugs for Psychiatric Disorders: A Systematic Review and Meta-Analysis

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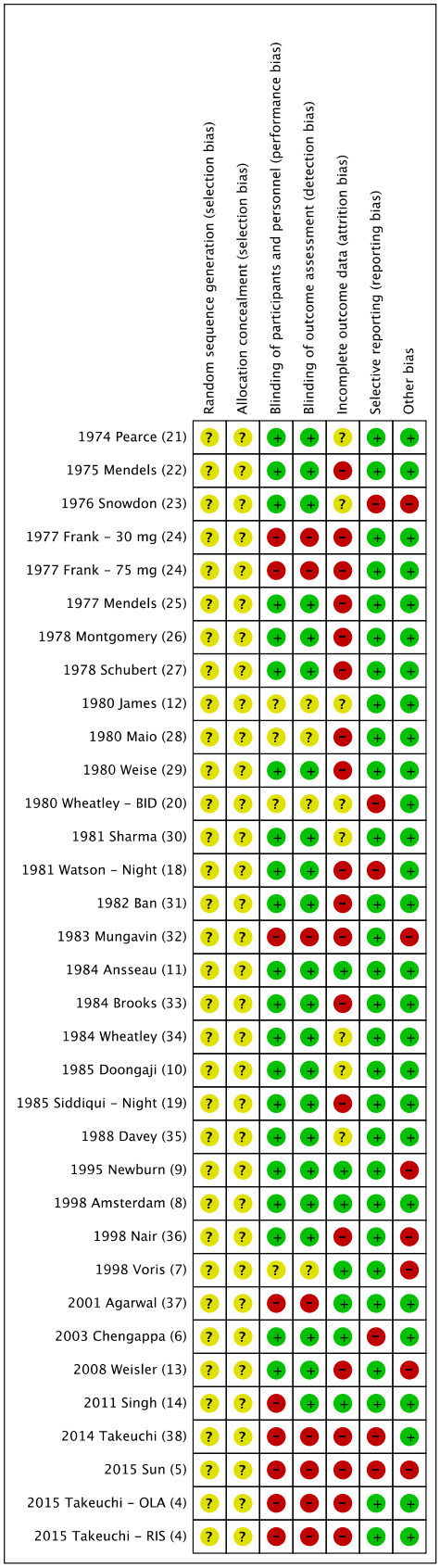
Supplementary Figure 1. Risk of Bias



Abbreviations: OLA, olanzapine; RIS, risperidone

Supplementary Table 1. Study Discontinuation and Psychopathology in Sensitivity Analysis

	Number of comparisons	Number of patients	Risk ratio			Heterogeneity	
			RR[a]	95% CI	*P*	*P*	I^2 (%)
Single vs. multiple daily dosing							
Study discontinuation due to all causes							
Double-blind studies	21	2366	1.02	0.94, 1.10	0.67	0.41	4
Non-double-blind studies	9	517	0.87	0.61, 1.25	0.45	0.58	0
Studies adopting intention-to-treat analysis	6	328	0.67	0.33, 1.37	0.27	0.61	0
Studies adopting modified intention-to-treat analysis	5	870	1.05	0.95, 1.15	0.34	0.84	0
Studies adopting completer analysis	13	904	0.96	0.71, 1.29	0.79	0.10	35
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	26	2395	1.01	0.93, 1.10	0.80	0.58	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	4	488	0.65	0.27, 1.54	0.32	0.11	55
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	23	2208	1.02	0.93, 1.11	0.71	0.46	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	7	675	1.01	0.85, 1.20	0.93	0.36	9
Study discontinuation due to lack of efficacy							
Double-blind studies	13	1790	1.07	0.85, 1.35	0.54	0.62	0
Non-double-blind studies	9	517	0.72	0.22, 2.32	0.58	0.56	0
Studies adopting intention-to-treat analysis	6	328	0.83	0.22, 3.11	0.78	0.81	0
Studies adopting modified intention-to-treat analysis	5	870	1.16	0.87, 1.55	0.31	0.62	0
Studies adopting completer analysis	8	626	1.72	0.66, 4.51	0.27	0.45	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	19	1885	1.11	0.86, 1.43	0.44	0.61	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	3	422	0.90	0.55, 1.48	0.68	0.80	0
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	15	1632	1.19	0.90, 1.57	0.22	0.80	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	7	675	0.83	0.55, 1.24	0.35	0.56	0
Study discontinuation due to adverse events							
Double-blind studies	16	2054	0.92	0.72, 1.16	0.46	0.70	0
Non-double-blind studies	9	517	0.97	0.60, 1.57	0.90	0.81	0
Studies adopting intention-to-treat analysis	6	328	0.64	0.20, 2.01	0.44	0.28	15
Studies adopting modified intention-to-treat analysis	5	870	1.14	0.82, 1.59	0.43	0.86	0
Studies adopting completer analysis	10	708	0.83	0.55, 1.26	0.39	0.71	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	22	2149	0.87	0.68, 1.10	0.24	0.94	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	3	422	0.73	0.13, 4.17	0.72	0.16	49
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	18	1896	0.91	0.71, 1.17	0.46	0.80	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	7	675	0.96	0.64, 1.44	0.85	0.62	0
Psychopathology							
Double-blind studies	5	1093	-0.02	-0.18, 0.13	0.76	0.20	33
Non-double-blind studies	3	244	0.05	-0.20, 0.30	0.68	0.77	0
Studies adopting intention-to-treat analysis	2	83	-0.16	-0.59, 0.27	0.48	0.67	0
Studies adopting modified intention-to-treat analysis	3	705	0.10	-0.05, 0.24	0.20	0.82	0
Studies adopting completer analysis	2	293	0.01	-0.22, 0.24	0.95	0.35	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	6	945	-0.04	-0.17, 0.08	0.50	0.50	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	2	392	0.11	-0.09, 0.31	0.28	0.37	0
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	7	1081	0.05	-0.07, 0.17	0.38	0.82	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	256	-0.22	-0.47, 0.02	0.08	NA	NA
Once vs. twice daily dosing							
Study discontinuation due to all causes							
All studies	16	1770	1.01	0.93, 1.09	0.82	0.61	0
Double-blind studies	11	1598	1.01	0.94, 1.09	0.74	0.66	0
Non-double-blind studies	5	172	0.51	0.20, 1.31	0.16	0.55	0
Studies adopting intention-to-treat analysis	4	119	0.47	0.14, 1.58	0.22	0.48	0
Studies adopting modified intention-to-treat analysis	5	870	1.05	0.95, 1.15	0.34	0.84	0
Studies adopting completer analysis	4	312	0.82	0.44, 1.53	0.54	0.27	24
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	12	1282	1.01	0.92, 1.10	0.86	0.75	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	4	488	0.65	0.27, 1.54	0.32	0.11	55
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	10	1284	1.01	0.92, 1.11	0.80	0.66	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	6	486	1.02	0.81, 1.29	0.85	0.27	23
Study discontinuation due to lack of efficacy							
All studies	14	1662	1.07	0.85, 1.34	0.59	0.68	0
Double-blind studies	9	1490	1.07	0.85, 1.35	0.57	0.53	0
Non-double-blind studies	5	172	0.96	0.24, 3.81	0.96	0.46	0
Studies adopting intention-to-treat analysis	4	119	0.83	0.22, 3.11	0.78	0.81	0
Studies adopting modified intention-to-treat analysis	5	870	1.16	0.87, 1.55	0.31	0.62	0
Studies adopting completer analysis	3	270	2.69	0.81, 8.93	0.11	0.88	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	11	1240	1.12	0.86, 1.45	0.41	0.54	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	3	422	0.90	0.55, 1.48	0.68	0.80	0
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	8	1176	1.21	0.91, 1.60	0.19	0.79	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	6	486	0.83	0.55, 1.24	0.35	0.56	0
Study discontinuation due to adverse events							
All studies	15	1704	0.98	0.76, 1.26	0.86	0.65	0
Double-blind studies	10	1532	0.98	0.76, 1.28	0.91	0.65	0
Non-double-blind studies	5	172	0.62	0.06, 6.95	0.70	0.19	43
Studies adopting intention-to-treat analysis	4	119	0.16	0.01, 2.77	0.21	NA	NA
Studies adopting modified intention-to-treat analysis	5	870	1.14	0.82, 1.59	0.43	0.86	0
Studies adopting completer analysis	4	312	0.79	0.31, 2.02	0.63	0.26	27
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	12	1282	0.90	0.66, 1.23	0.51	0.75	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	3	422	0.73	0.13, 4.17	0.72	0.16	49
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	9	1218	0.96	0.71, 1.31	0.82	0.50	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	6	486	1.01	0.64, 1.59	0.98	0.49	0
Psychopathology							
All studies	7	1197	-0.01	-0.13, 0.10	0.81	0.40	3
Double-blind studies	5	1093	-0.02	-0.18, 0.13	0.76	0.20	33
Non-double-blind studies	2	104	-0.04	-0.43, 0.35	0.84	0.70	0
Studies adopting intention-to-treat analysis	2	83	-0.16	-0.59, 0.27	0.48	0.67	0
Studies adopting modified intention-to-treat analysis	3	705	0.10	-0.05, 0.24	0.20	0.82	0
Studies adopting completer analysis	1	153	-0.10	-0.42, 0.22	0.54	NA	NA
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	5	805	-0.07	-0.21, 0.07	0.30	0.52	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	2	392	0.11	-0.09, 0.31	0.28	0.37	0
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	6	941	0.04	-0.08, 0.17	0.51	0.75	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	256	-0.22	-0.47, 0.02	0.08	NA	NA
Once vs. three times daily dosing							
Study discontinuation due to all causes							
All studies	13	1073	1.02	0.80, 1.31	0.87	0.28	16
Double-blind studies	9	728	0.99	0.69, 1.41	0.95	0.14	36
Non-double-blind studies	4	345	0.95	0.65, 1.40	0.81	0.55	0
Studies adopting intention-to-treat analysis	2	209	0.81	0.33, 1.96	0.64	NA	NA
Studies adopting modified intention-to-treat analysis	0	0	NE	NE	NA	NA	NA
Studies adopting completer analysis	8	552	1.03	0.71, 1.50	0.86	0.08	44
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	13	1073	1.02	0.80, 1.31	0.87	0.28	16
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	0	0	NE	NE	NA	NA	NA
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	12	884	1.03	0.79, 1.35	0.81	0.24	22
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	189	0.81	0.33, 1.96	0.64	NA	NA
Study discontinuation due to lack of efficacy							
All studies	8	645	0.76	0.14, 4.14	0.75	0.30	9
Double-blind studies	4	300	1.86	0.18, 19.38	0.60	NA	NA
Non-double-blind studies	4	345	0.33	0.03, 3.12	0.33	NA	NA
Studies adopting intention-to-treat analysis	2	209	NE	NE	NA	NA	NA
Studies adopting modified intention-to-treat analysis	0	0	NE	NE	NA	NA	NA
Studies adopting completer analysis	5	356	0.76	0.14, 4.14	0.75	0.30	9
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	8	645	0.76	0.14, 4.14	0.75	0.30	9
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	0	0	NE	NE	NA	NA	NA
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	7	456	0.76	0.14, 4.14	0.75	0.30	9
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	189	NE	NE	NA	NA	NA
Study discontinuation due to adverse events							
All studies	9	827	0.85	0.58, 1.24	0.39	0.88	0
Double-blind studies	5	482	0.69	0.39, 1.22	0.20	0.63	0
Non-double-blind studies	4	345	0.99	0.60, 1.64	0.98	0.94	0
Studies adopting intention-to-treat analysis	2	209	0.81	0.33, 1.96	0.64	NA	NA
Studies adopting modified intention-to-treat analysis	0	0	NE	NE	NA	NA	NA
Studies adopting completer analysis	5	356	0.96	0.57, 1.60	0.87	0.82	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	9	827	0.85	0.58, 1.24	0.39	0.88	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	0	0	NE	NE	NA	NA	NA
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	8	638	0.86	0.56, 1.30	0.47	0.81	0
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	189	0.81	0.33, 1.96	0.64	NA	NA
Psychopathology							
All studies	1	140	0.12	-0.21, 0.45	0.47	NA	NA
Double-blind studies	0	0	NE	NE	NA	NA	NA
Non-double-blind studies	1	140	0.12	-0.21, 0.45	0.47	NA	NA
Studies adopting intention-to-treat analysis	0	0	NE	NE	NA	NA	NA
Studies adopting modified intention-to-treat analysis	0	0	NE	NE	NA	NA	NA
Studies adopting completer analysis	1	140	0.12	-0.21, 0.45	0.47	NA	NA
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	1	140	0.12	-0.21, 0.45	0.47	NA	NA
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	0	0	NE	NE	NA	NA	NA
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	140	0.12	-0.21, 0.45	0.47	NA	NA
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	0	0	NE	NE	NA	NA	NA

[a]RR >1 means favours MDD.

Abbreviations: NA, not applicable; NE, not estimable; RR, risk ratio

Supplementary Table 2. Treatment-Emergent Adverse Events With Significant Difference in Sensitivity Analysis

	Number of comparisons	Number of patients	Risk ratio			Heterogeneity	
			RR[a]	95% CI	*P*	*P*	I^2 (%)
Single vs. multiple daily dosing							
Anxiety							
Double-blind studies	3	303	0.51	0.31, 0.83	**0.008**	0.79	0
Studies adopting completer analysis	2	251	0.51	0.31, 0.85	**0.009**	0.49	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	4	347	0.53	0.33, 0.84	**0.007**	0.89	0
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	3	295	0.53	0.33, 0.85	**0.008**	0.73	0
Decreased sexual orgasm							
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	257	1.76	1.05, 2.95	**0.03**	NA	NA
Diziness							
Studies adopting intention-to-treat analysis	1	189	3.64	1.41, 9.40	**0.008**	NA	NA
Drowsiness							
Double-blind studies	5	361	2.02	1.09, 3.75	**0.03**	0.85	0
Orthostatic faintness							
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	2	402	0.61	0.40, 0.94	**0.02**	0.72	0
Sleepiness							
Double-blind studies	3	934	0.82	0.68, 0.99	**0.04**	0.27	23
Studies adopting modified intention-to-treat analysis	2	677	0.75	0.62, 0.91	**0.004**	0.97	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	1	336	0.75	0.58, 0.97	**0.03**	NA	NA
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	2	677	0.75	0.62, 0.91	**0.004**	0.97	0
Once vs. twice daily dosing							
Anxiety							
All studies	4	347	0.53	0.33, 0.84	**0.007**	0.63	0
Double-blind studies	3	303	0.51	0.31, 0.83	**0.008**	0.79	0
Studies adopting completer analysis	2	251	0.51	0.31, 0.85	**0.009**	0.49	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	4	347	0.53	0.33, 0.84	**0.007**	0.89	0
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	3	295	0.53	0.33, 0.85	**0.008**	0.73	0
Decreased sexual orgasm							
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	257	1.76	1.05, 2.95	**0.03**	NA	NA
Diziness							
No significant difference							
Drowsiness							
No significant difference							
Orthostatic faintness							
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	2	402	0.61	0.40, 0.94	**0.02**	0.72	0
Sleepiness							
All studies	3	934	0.82	0.68, 0.99	**0.04**	0.27	23
Double-blind studies	3	934	0.82	0.68, 0.99	**0.04**	0.27	23
Studies adopting modified intention-to-treat analysis	2	677	0.75	0.62, 0.91	**0.004**	0.97	0
Studies examining psychotropic drugs with peripheral elimination half-life ≥24 hours	1	336	0.75	0.58, 0.97	**0.03**	NA	NA
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	2	677	0.75	0.62, 0.91	**0.004**	0.97	0
Once vs. three times daily dosing							
Anxiety							
No significant difference							
Decreased sexual orgasm							
No significant difference							
Diziness							
Non-double-blind studies	2	249	0.26	0.08, 0.84	**0.02**	0.65	0
Studies adopting intention-to-treat analysis	1	189	3.64	1.41, 9.40	**0.008**	NA	NA
Studies examining psychotropic drugs without the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	1	189	3.64	1.41, 9.40	**0.008**	NA	NA
Drowsiness							
All studies	4	464	2.78	1.27, 6.06	**0.01**	0.81	0
Double-blind studies	2	215	2.54	1.06, 6.05	**0.04**	0.46	0
Studies examining psychotropic drugs with peripheral elimination half-life <24 hours	4	464	2.78	1.27, 6.06	**0.01**	0.81	0
Studies examining psychotropic drugs with the description that the drug should be administered once daily (i.e., Single-DD) in the product monograph	4	464	2.78	1.27, 6.06	**0.01**	0.81	0
Orthostatic faintness							
No significant difference							
Sleepiness							
No significant difference							

[a] RR >1 means favours Multiple-DD.

Bold number means statistically significant.

Abbreviations: NA, not applicable; RR, risk ratio