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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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1974 Pearce (21)	?	?	+	+	?	+	+
1975 Mendels (22)	?	?	+	+	-	+	+
1976 Snowdon (23)	?	?	+	+	?	-	-
1977 Frank - 30 mg (24)	?	?	-	-	-	+	+
1977 Frank - 75 mg (24)	?	?	-	-	-	+	+
1977 Mendels (25)	?	?	+	+	-	+	+
1978 Montgomery (26)	?	?	+	+	-	+	+
1978 Schubert (27)	?	?	+	+	-	+	+
1980 James (12)	?	?	?	?	?	+	+
1980 Maio (28)	?	?	?	?	-	+	+
1980 Weise (29)	?	?	+	+	-	+	+
1980 Wheatley - BID (20)	?	?	?	?	?	-	+
1981 Sharma (30)	?	?	+	+	?	+	+
1981 Watson - Night (18)	?	?	+	+	-	-	+
1982 Ban (31)	?	?	+	+	-	+	+
1983 Mungavin (32)	?	?	-	-	-	+	-
1984 Ansseau (11)	?	?	+	+	+	+	+
1984 Brooks (33)	?	?	+	+	-	+	+
1984 Wheatley (34)	?	?	+	+	?	+	+
1985 Doongaji (10)	?	?	+	+	?	+	+
1985 Siddiqui - Night (19)	?	?	+	+	-	+	+
1988 Davey (35)	?	?	+	+	?	+	+
1995 Newburn (9)	?	?	+	+	+	+	-
1998 Amsterdam (8)	?	?	+	+	+	+	+
1998 Nair (36)	?	?	+	+	-	+	-
1998 Voris (7)	?	?	?	?	+	+	-
2001 Agarwal (37)	?	?	-	-	+	+	+
2003 Chengappa (6)	?	?	+	+	+	-	+
2008 Weisler (13)	?	?	+	+	-	+	-
2011 Singh (14)	?	?	-	+	+	+	+
2014 Takeuchi (38)	?	?	-	-	-	-	+
2015 Sun (5)	?	?	-	-	-	-	-
2015 Takeuchi - OLA (4)	?	?	-	-	-	+	+
2015 Takeuchi - RIS (4)	?	?	-	-	-	+	+

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	I ²	P	
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	0.81, 1.26	0.45	0.58	0
Studies adopting intention-to-treat analysis	6	328	0.87	0.33, 1.37	0.27	0.81	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	0.85	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-DO) 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-DO) 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-DO) 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-DO) 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	0.38	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-DO) 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-DO) 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	-0.58, 0.27	0.48	0.57	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-DO) 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-DO) 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	0.56	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	0.64	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-DO) 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-DO) 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	1652	1.07	0.85, 1.34	0.59	0.68	0
Double-blind studies	9	1490	1.07	0.85, 1.35	0.57	0.63	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	16
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-DO) 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-DO) 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	0.82	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-DO) 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-DO) 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	-0.58, 0.27	0.48	0.57	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	163	-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-DO) 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-DO) 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	0.89, 1.41	0.85	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	852	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-DO) 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-DO) 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	0.16, 19.39	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-DO) 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-DO) 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-DO) 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-DO) 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-DO) 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-DO) in the product monograph	0	0	NE	NE	NA	NA	NA

RR >1 means favours MOD.
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
Dizziness							
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
Dizziness							
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							
Dizziness							
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