Effects of antipsychotics on heart rate in treatment of schizophrenia: a systematic review and meta-analysis

Maximilian Huhn¹⁰, Thomas Arndt, Johannes Schneider-Thoma and Stefan Leucht

Abstract

Background: Antipsychotics are the treatment of choice in the therapy of schizophrenia. These drugs can be associated with changes in heart rate, but this question has never been examined systematically.

Objective: We aimed to analyse changes in heart rate during treatment with antipsychotics using the frequency of tachycardia and bradycardia events.

Design: For this systematic review and meta-analysis, we included all randomized controlled trials for the acute treatment of schizophrenia comparing antipsychotics head-to-head or with placebo. **Data Sources and Methods:** We searched Embase, MEDLINE, PsycINFO, PubMed, BIOSIS, Cochrane Central Register of Controlled Trials (CENTRAL), WHO International Clinical Trials Registry Platform and ClinicalTrials.gov (last search June 2021). Two authors independently selected studies and extracted data. We conducted pairwise meta-analyses using a random-effects model. Outcomes were tachycardia and bradycardia events.

Results: We found 469 trials meeting the inclusion criteria. Seventy-seven studies with 16,907 participants provided data on tachycardia or bradycardia events. We found no significant differences between antipsychotics and placebo or between antipsychotics for bradycardia events based on sparse data. Antipsychotics had a higher risk for tachycardia events compared with placebo [N = 37, n = 7827, risk ratio (RR) = 1.83, 95% confidence interval (CI) = 1.40–2.41], with large differences between the individual substances (iloperidone RR = 14.05, chlorpromazine RR = 4.84, loxapine RR = 4.52, risperidone RR = 3.38, quetiapine RR = 2.64, paliperidone RR = 1.65]. Some head-to-head comparisons were also significantly different: olanzapine *versus* haloperidol RR = 2.87, chlorpromazine *versus* thiothixene RR = 2.92, quetiapine *versus* lurasidone RR = 3.22, risperidone *versus* aripiprazole RR = 4.37, iloperidone *versus* ziprasidone RR = 4.65].

Conclusion: Many studies do not report data for cardiac outcomes, but the available evidence indicates that treatment with antipsychotics raises the risk for tachycardia. Therefore, especially patients with cardiac risk factors should be monitored closely during antipsychotic treatment. **Registration:** PROSPERO: CRD42014014919

Keywords: schizophrenia, antipsychotics, meta-analysis, tachycardia, bradycardia

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Introduction

Schizophrenia is a debilitating disease with a huge burden for patients and their relatives.¹ Antipsychotics are the treatment of choice, but can cause severe side effects.² Some antipsychotics (e.g. clozapine and olanzapine) are associated with higher cardiometabolic risks compared with other (e.g. aripiprazole).³ There is evidence that people with schizophrenia have a higher risk of cardiovascular disease–related deaths compared with the general population, which maybe increased by the use of antipsychotics.⁴ Furthermore, patients with schizophrenia often have many risk factors for cardiovascular events such as tobacco addiction or metabolic syndrome.⁵ Often, they do not seek medical treatment at all⁶

Meta-analysis

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and there is evidence that they obtain fewer cardiac interventions than the general population.⁷ A large cohort study found that second-generation antipsychotic agents raise the risk of sudden cardiac death.8 These drugs influence repolarisation and heart rate, which can result in fatal arrhythmias.9 In general, higher heart rates are associated with a higher mortality due to cardiovascular diseases even in the general population.¹⁰ In the past, several retrospective trials have examined the risk for cardiac events during antipsychotic treatment and the prolongation of the OTc interval. But the evidence of randomized clinical trials in terms of heart rate has never been summarized systematically. We therefore aim to systematically summarize the available evidence of this cardiac side effect in randomized controlled trials of acute treatment of schizophrenia.

Methods

This analysis follows the PRISMA-Guideline¹¹ and is part of a larger already published project² (PRISMA checklist Supplemental Appendix 1). The according protocol was registered *a priori* at PROSPERO under the registration number: CRD42014014919 (Supplemental Appendix 2).

Participants and interventions

We included randomized controlled trials (RCTs) in adults with acute symptoms of schizophrenia or related disorders (such as schizophreniform or schizoaffective disorders). We excluded studies in patients with treatment resistance, first episode, predominant negative or depressive symptoms, concomitant medical illnesses and relapse-prevention studies. We included trials with a minimum duration of 3 weeks. Interventions were all second-generation antipsychotics approved in Europe or the United States and placebo. Based on a survey among 50 international schizophrenia experts,¹² we also included the following older antipsychotics: benperidol, chlorpromazine, clopenthixol, flupenthixol, fluphenazine, haloperidol, levomepromazine, loxapine, molindone, penfluridol, perazine, perphenazine, pimozide, sulpiride, thioridazine, thiothixene, trifluoperazine and zuclopenthixol. Intramuscular formulations were excluded as they are mainly used for relapse prevention (long-acting) or in emergency situations (short-term). We included target to maximum doses according to the 'International Consensus Study of Antipsychotics' for flexible

dose studies.¹³ We included all flexible dose studies because investigators can titrate the dose for the individual patient. As the examined outcomes are based on the objective measurement of heart rates, we included double-blind, single-blind and open studies, but excluded open studies in a sensitivity analysis. Studies from mainland China were excluded due to quality concerns.¹⁴ We excluded studies with high risk of bias for randomization and allocation.

Search

We searched the following databases without language restrictions: Medline, Cochrane Central register of Controlled Trials (CENTRAL), Embase, Biosis, PsycINFO, Pubmed, Clinicaltrials. gov and WHO International Trial Registry. The references of included studies were screened for additional studies. The search strategy was based on the update of a previously conducted analysis and the full search strategy is presented in the supplement (last search June 2021, Supplemental Appendix 3).

Outcomes

We extracted bradycardias and tachycardias reported as adverse events as stated by the original authors, but also reported with the adverse event terms 'low heart frequency' and 'low pulse' or 'high heart frequency' and 'high pulse rate'.

Data extraction and analysis

At least two reviewers (MH, TA, JST, Natalie Peters, Lio Baeckers, Angelika Kapfhammer, Dongfang Wang and Shimeng Dong) screened the search results independently, retrieved fulltext articles, and checked inclusion criteria. In case of doubt, a third reviewer (SL) was involved. Two reviewers independently extracted data and entered them in electronic forms in Microsoft Access 2010 (MH, TA, JST, Natalie Peters and Lio Baeckers). An algorithm checked for conflicting data entries.

We calculated pairwise random-effects metaanalyses combining the event rates in intervention and control groups.¹⁵ Effect sizes were risk ratios and number-needed-to-harm (NNTH). All effect sizes were presented along with their 95% confidence intervals (CIs). We assessed between study heterogeneity with the I²-statistic and the chisquare test for homogeneity, with I² > 50% and chi-square p < 0.05 indicating significant heterogeneity.¹⁶ We used contour-enhanced funnel plots¹⁷ and the trim and fill method¹⁸ to explore small trial bias, if at least 10 studies were available. All statistical analysis were conducted with the statistical programme R version 3.6.1¹⁹ using the package meta.²⁰ The *p* values lower than 0.05 were considered statistically significant.

Sensitivity analysis

We excluded open and single-blind studies in a sensitivity analysis. We also applied a fixed-effects model and checked for probable changes when a random-effects model was applied. We decided post hoc to exclude long-term studies (duration >13 weeks) in a sensitivity analysis to check for higher event rates in short-term studies.

Risk of bias

Risk of bias was assessed independently by two reviewers (Maximilian Huhn, Thomas Arndt, Natalie Peter, Lio Baeckers and Johannes Schneider) using the criteria stated by the Cochrane Collaboration²¹ (Supplemental Appendix 6).

Results

Descriptives of the sample

The searches resulted in 55,097 hits. After elimination of duplications, titles and abstracts were screened for matching the inclusion criteria and 3283 full texts retrieved. After full-text screening, 77 studies with 16,907 participants provided data on bradycardia or tachycardia events. The detailed PRISMA flowchart can be found in Figure 1. A detailed list of the included studies can be found in Supplemental Appendix 4. The studies were published between 1968 and 2019. Seventy-three studies were double-blind, two single-blind and two open. Mean trial duration was 8 (SD = 5.94) weeks. Thirty-nine studies were placebo controlled. The sample had the following characteristics: 10,372 participants were male and 6535 female. Mean age was 37.34 (SD = 4.12) years and the duration of illness in years was 12.80 (SD = 5.94).

Bradycardia

Seventeen studies with 6866 participants reported data for bradycardia events. Bradycardias were overall quite rare and reported for 0.4% of patients. Eight studies with 2363 participants reported bradycardia events for the comparison of antipsychotics with placebo. The overall risk ratio of antipsychotics compared with placebo was not significant [N = 8, n = 2363, risk ratio(RR) = 1.83, 95% confidence interval (CI) = 0.56-5.96, p = 0.32 [Figure 2(a)]. There was no significant difference between haloperidol and placebo (N = 3, n = 429, RR = 3.57, 95% CI = 0.75-16.99, p = 0.11) and lurasidone and placebo (N = 3, n = 1220, RR = 1.81, 95% CI = 0.30-11.0, p = 0.52) [Figure 2(b)]. The comparisons of loxapine, olanzapine, quetiapine, risperidone and ziprasidone could not be calculated because there were no events in both arms.

The comparison of haloperidol with amisulpride/olanzapine/ziprasidone showed no significant difference for the pooled comparison (N = 8,n = 3983, RR = 2.03,95% CI = 0.66-6.27, p = 0.22) nor for the comparison with olanzapine (N = 2, n = 2198,RR = 5.92, 95% CI = 0.62–56.56, p = 0.12) or ziprasidone (N = 5, n = 1586, RR = 1.62, 95% CI = 0.37-7.11, p = 0.52) or amisulpride (N = 1, n = 199, RR = 0.90, 95% CI = 0.06-14.11, p = 0.94) alone [Figure 2(c)]. We found also no significant differences for lurasidone, perphenazine, quetiapine and risperidone compared with other drugs.

Tachycardia

Seventy-three studies with 15,732 participants reported data for tachycardia events. Tachycardias were reported for 4.8% of patients. Treatment with antipsychotics had a significant higher risk for tachycardias than placebo (N = 37, n = 7827, RR = 1.83, 95% CI = 1.40–2.41, p < 0.001, NNTH = 43) [Figure 3(a)], but there were large differences between the individual substances. The following drugs had a higher relative risk for tachycardia compared with placebo. The ranking is from highest to lowest risk RR: iloperidone 14.05 (95% CI = 1.93-102.26, p < 0.01), chlor-CI = 1.82 - 18.29, promazine 4.84(95%) p = 0.02), loxapine 4.52 (95% CI = 1.06–19.28, p = 0.04), risperidone 3.27 (95% CI = 1.11-10.32, p = 0.03), quetiapine 2.64 (95%) CI = 1.13-6.16, p = 0.02), paliperidone 1.65 (95% CI = 1.08-2.51, p = 0.02) [Figure 3(b)]. We found no significant differences for the following antipsychotics: aripiprazole, fluphenazine, haloperidol, loxapine, lurasidone, olanzapine, perphenazine, thioridazine, trifluoperazine,





ziprasidone and zotepine [Figure 3(b)]. The following antipsychotics differed significantly from each other: aripiprazole was better than risperidone: RR 0.23 (95% CI = 0.1-0.541, p < 0.01), haloperidol better than olanzapine: RR 0.35 (95% CI = 0.13-0.95, p = 0.04), lurasidone better than quetiapine: RR 0.31 (95% CI = 0.12– 0.78, p = 0.01), thiothixene better than chlorpromazine: RR 0.34 (95% CI = 0.14–0.85, p = 0.02) and ziprasidone better than iloperidone: RR 0.21 (95% CI = 0.07–0.7, p = 0.01) [Figure 3(c)].

(a)	Antipsyc	hotic	Pla	acebo				
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	Weight
Beasley 1996b	1	202	0	68		1.01	[0.04; 24.62]	13.7%
Clark 1977b	0	25	0	13				0.0%
Garcia 2009	4	60	1	64		4.27	[0.49; 37.10]	29.9%
Higuchi 2019a	2	305	0	152		- 2.50	[0.12; 51.67]	15.2%
Higuchi 2019b	1	327	0	133		1.22	[0.05; 29.83]	13.7%
Loebel 2013	1	366	0	122		1.00	[0.04; 24.45]	13.7%
Schmidt 2014	0	93	0	101				0.0%
Study 115 2000	1	249	0	83	+	1.00	[0.04; 24.41]	13.7%
Random effects mode Heterogeneity: $I^2 = 0\%$, τ^2	$p^{2} = 0, p = 0$	1627).95		736		1.83	[0.56; 5.96]	100.0%
					0.1 0.5 1 2 10			
				6				

favors antipsychotic favors placebo

Study	Antipsycl Events	hotic Total	Pla Events	cebo Total	Risk Ratio	RR	95%-CI
Antipsychotic = Halop Beasley 1996b Garcia 2009 Study 115 2000 Random effects mode Heterogeneity: $J^2 = 0\%$, τ^2	eridol 1 4 1 ² = 0, p = 0.	69 60 85 214 97	0 1 0	68 64 83 215	*	- 2.96 4.27 - 2.93 3.57	[0.12; 71.33] [0.49; 37.10] [0.12; 70.90] [0.75; 16.99]
Antipsychotic = Olanz Beasley 1996b Schmidt 2014 Random effects mode Heterogeneity: not applica	apine 0 1 able	133 93 226	0 0	68 101 169			
Antipsychotic = Luras Loebel 2013 Higuchi 2019a Higuchi 2019b Random effects mode Heterogeneity: $l^2 = 0\%$, τ^2	idone 1 2 1 ¹ ² = 0, p = 0.	246 305 262 813 97	0 0 0	122 152 133 407		1.49 2.50 1.53 1.81	[0.06; 36.33] [0.12; 51.67] [0.06; 37.20] [0.30; 11.04]
Antipsychotic = Rispe Higuchi 2019b Random effects mode Heterogeneity: not applica	ridone 0 I able	65 65	0	133 133			
Antipsychotic = Loxap Clark 1977b Random effects mode Heterogeneity: not applica	oine O I able	25 25	0	13 13			
Antipsychotic = Zipras Study 115 2000 Random effects mode Heterogeneity: not applica	sidone 0 I able	164 164	0	83 83			
Antipsychotic = Quetia Loebel 2013 Random effects mode Heterogeneity: not applica	apine 0 I	120 120	0	122 122			
Heterogeneity: $I^2 = 0\%$, τ^2	$c^{2} = 0, p = 0.$	99			01 051 2 10		
				four	e antinevelatic favore placebo		

favors antipsychotic favors placebo

(b)

Figure 2. (Continued)

(c)	Interve	ntion	Co	ntrol	Dick Datio	DD	05% CI
Study	Events	TUtai	Events	TOtal	RISK Ratio	KK	95%-CI
Intervention = Haloperidol							
A1281050 Ziprasidone	0	122	1	130		0.36	[0.01; 8.63]
Beasley 1996b Olanzapine	1	69	0	133		5.76	[0.24; 139.61]
Brook 2005 Ziprasidone	1	138	1	429		3.11	[0.20; 49.37]
Goff 1998 Ziprasidone	0	1/	0	20		F 77	10 24: 440 401
Study 115 2000 Ziprasidone Protocol 129–201 1907 Ziprasidono	1	220	1	104		5.//	[0.24; 140.18]
Tollefson 1997 Olanzanine	1	230		1336		6.07	[0.00, 10.23]
Carrière 2000 Amisulpride	- 1	105	1	0/		0.07	[0.25, 140.01]
Random effects model		1434		2549		2.03	[0.66: 6.27]
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $p = 0.80$)	1101		2010	~	2100	[olooj olzij
Intervention = Olanzapine							
Breier 2005 Ziprasidone	1	277	0	271		2.94	[0.12; 71.74]
Naukkarinen 2000 Perphenazine	0	23	1	23		0.33	[0.01; 7.77]
Beasley 1996b Haloperidol	0	133	1	69		0.17	[0.01; 4.20]
Mortimer 2004 Amisulpride	0	188	5	189		0.09	[0.01; 1.64]
Dendem effects model	0	1330	1	4040		0.16	[0.01; 4.04]
Haterogeneity $l^2 = 0\%$ $\tau^2 = 0$ $p = 0.51$		1957		1212	\sim	0.29	[0.07; 1.10]
Heterogeneity. $T = 0\%$, $t = 0$, $p = 0.56$	2						
Intervention = Amisulpride							
Carrière 2000 Haloperidol	1	94	1	105		1.12	[0.07; 17.61]
Mortimer 2004 Olanzapine	5	189	0	188		10.94	[0.61; 196.49]
Random effects model		283		293		3.36	[0.33; 34.08]
Heterogeneity: $I^2 = 26\%$, $\tau^2 = 0.7209$, μ) = 0.25						
Intervention - Lurasidana							
Lookel 2012 Quetionine	4	246	0	120		1 47	10.06: 25.721
Loepei 2013 Queuapine		240	0	120		0.75	[0.00, 30.73]
Random effects model		502	0	185		1.05	[0.03, 10.17]
Heterogeneity: $J^2 = 0\%$ $\tau^2 = 0$ $p = 0.77$	7	500		105		1.05	[0.11, 10.00]
110000g0100g11 = 010, 1 = 0, p = 0.11							
Intervention = Risperidone							
Higuchi 2019b Lurasidone	0	65	1	262		1.34	[0.06; 32.42]
Random effects model		65		262		1.34	[0.06; 32.42]
Heterogeneity: not applicable							
Intervention - Zinnesidens							
A1291050 Haloporidal	1	120	0	122		2 02	10 12: 69 471
Rejer 2005 Olanzanine		271	1	277		0.34	[0.12, 00.47]
Brook 2005 Haloperidol	1	429	1	138		0.34	[0.02: 5.11]
Goff 1998 Haloperidol	o	20	ò	17	_	0.02	[0.02, 0.11]
Study 115 2000 Haloperidol	ō	164	1	85		0.17	[0.01: 4.21]
Protocol 128-301 1997 Haloperidol	1	243	1	238	ŧ	0.98	[0.06; 15.57]
Random effects model		1257		877	\sim	0.56	[0.15; 2.12]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.75$	5						
Intervention = Perphenazine		22	•	22	_	2.00	10 40. 00 001
Naukkarinen 2000 Olanzapine	1	23	0	23		3.00	[0.13, 69.95]
Kanuom enects model		ZJ		20		5.00	[0.15; 09.95]
i istorogeneity, not applicable							
Intervention = Quetiapine							
Loebel 2013 Lurasidone	0	120	1	246		0.68	[0.03; 16.61]
Random effects model		120		246		0.68	[0.03; 16.61]
Heterogeneity: not applicable							
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.84$	4						
				-	0.01 0.1 1 10 100		
				fav	ors intervention favors control		

Figure 2. (a) Antipsychotic drugs *versus* placebo (overall) – bradycardia events. (b) Antipsychotic drugs *versus* placebo (individual antipsychotics) – bradycardia events. (c) Antipsychotic drugs head-to-head comparison – bradycardia events.

(a)	Antipsychotic	Placebo			
Study	Events Total E	Events Total	Risk Ratio	RR	95%-CI Weight
short-term (3-13 wee	ks)				-
Beasley 1996b	9 202	1 68		3.03	[0.39; 23.48] 1.8%
Borison 1992	1 106	0 54	4	1.54	[0.06: 37.06] 0.7%
Borison 1996	3 54	1 55		3.06	[0.33; 28.47] 1.5%
Cantillon 2014	1 20	0 39		5.78	[0.25; 135.68] 0.7%
Chouinard 1975	0 24	1 24		0.33	[0.01; 7.79] 0.7%
Clark 1971a	1 65	0 21		0.98	[0.04; 23.29] 0.7%
Clark 1972	18 37	1 18		8.76	[1.27; 60.53] 2.0%
Clark 1977a	1 9	0 9		3.00	[0.14; 64.73] 0.8%
Clark 1977b	4 25	1 13		2.08	[0.26; 16.75] 1.7%
Cooper 2000a	3 106	0 53		3.52	[0.18; 66.84] 0.8%
Coppola 2011	2 70	0 65		4.65	[0.23; 94.97] 0.8%
Cutler 2008	31 454	1 152		10.38	[1.43; 75.38] 1.9%
Daniel 1999	2 104	2 92		0.88	[0.13; 6.15] 2.0%
Davidson 2007	24 253	10 123		1.17	[0.58; 2.36] 14.8%
Durgam 2015	0 152	0 153			0.0%
Egan 2013	3 47	1 83		5.30	[0.57; 49.50] 1.5%
Fabre 1995	38	1 4		1.50	[0.22; 10.22] 2.0%
Geffen 2012	9 91	11 93		0.84	[0.36; 1.92] 10.6%
Higuchi 2019b	2 327	0 133		2.04	[0.10; 42.17] 0.8%
Hirayasu 2010	2 183	0 138		3.77	[0.18; 77.98] 0.8%
Kane 2007b	86 503	13 127		1.67	[0.96; 2.89] 24.3%
Keck 1998	2 47	0 48		5.11	[0.25; 103.56] 0.8%
Liebermann 2015	9 82	1 85		9.33	[1.21; 72.01] 1.8%
Lindenmayer 2008	27 267	2 84		4.25	[1.03; 17.49] 3.7%
Litman 2016	1 31	3 55		0.59	[0.06; 5.44] 1.5%
Loebel 2013	18 366	0 122		12.37	[0.75; 203.69] 0.9%
Marder 1994	4 130	0 66		4.59	[0.25; 83.92] 0.9%
Marder 2007c	16 334	3 110		1.76	[0.52; 5.91] 5.0%
NC100563706	2 43	0 37		4.31	[0.21; 86.99] 0.8%
Potkin 2003	22 301	1 103		7.53	[1.03; 55.15] 1.9%
Schmidt 2014	1 93	3 101		0.36	[0.04; 3.42] 1.5%
Snen 2014	0 //	0 78		4.40	0.0%
Small 1997	7 96	5 96		1.40	[0.46; 4.26] 5.9%
Study 115 2000	6 249 1 27	1 83		2.00	[0.24; 16.37] 1.7%
Denders offecte mede	J 3/	2650		4.00	[0.25, 142.01] 0.7%
Random effects mode	2 0 - 0 00	2009	\ Ŷ	1.05	[1.59; 2.41] 97.9%
Heterogeneity: $T = 0\%$, t	= 0, p = 0.60				
long-term (>13 weeks	5)				
Clark 1968b	2 36	0 18		2.53	[0.13; 50.11] 0.8%
Cooper 2000b	2 63	1 58		1.84	[0.17; 19.77] 1.3%
Random effects mode	al 99	76		2.08	[0.33; 13.36] 2.1%
Heterogeneity: $I^2 = 0\%$, τ^2	² = 0, p = 0.87				
Random effects mode	el 5092	2735	•	1.83	[1.40; 2.41] 100.0%
Heterogeneity: $I^2 = 0\%$, τ	$^{2} = 0, p = 0.69$. ,
		0.	01 0.1 1 10 100		
		favors	antipsychotic favors placebo		

Figure 3. (Continued)

(b) Study	Intervention Events Total I	Control Events Total	Risk Ratio	RR 95%-CI	
Intervention = Aripipraz Durgam 2015 Potkin 2003 Cantillon 2014 Random effects model Heterogeneity: $I^2 = 0\%$, τ^2 :	0 152 7 202 1 20 374 = 0, p = 0.80	0 153 1 103 0 39 295		3.57 [0.45; 28.62] 5.78 [0.25; 135.68] 4.13 [0.73; 23.48]	
Intervention = Chlorpro Clark 1971a Clark 1972 Clark 1972 Clark 1977a Cooper 2000a Clark 1968b Random effects model Heterogeneity: / ² = 0%, c ² s	mazine 0 23 9 19 1 53 1 53 1 18 122 = 0, p = 0.90	0 21 1 18 0 9 0 53 0 18 119		8.53 [1.20; 60.70] 3.00 [0.14; 64.73] 3.00 [0.12; 72.00] 3.00 [0.13; 68.97] 4.84 [1.28; 18.29]	
Intervention = Fluphena Clark 1971a Random effects model Heterogeneity: not applicab	azine 1 20 20	0 21 21	-	3.15 [0.14; 72.90] 3.15 [0.14; 72.90]	
Intervention = Haloperie Beasley 1996b Marder 1994 Study 115 2000 Borison 1992 Random effects model Heterogeneity: / ² = 0%, τ ² =	dol 1 69 1 66 2 85 1 53 273 = 0, p = 0.94	1 68 0 66 1 83 0 54 271		0.99 [0.06; 15.44] 3.00 [0.12; 72.32] 1.95 [0.18; 21.13] 3.06 [0.13; 73.36] 1.94 [0.48; 7.91]	
Intervention = Iloperido Cutler 2008 Random effects model Heterogeneity: not applicab	ne 28 303 303	1 152 152		14.05 [1.93; 102.26] 14.05 [1.93; 102.26]	
Intervention = Loxapine Clark 1972 Clark 1977b Random effects model Heterogeneity: l^2 = 3%, τ^2 =	9 18 4 25 43 = 0.0318. p = 0.3	1 18 1 13 31		9.00 [1.27; 63.89] 2.08 [0.26; 16.75] 4.52 [1.06; 19.28]	
Intervention = Lurasido Loebel 2013 Higuchi 2019b Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	ne 7 246 1 262 508 = 0, p = 0.45	0 122 0 133 255		7.45 [0.43; 129.45] 1.53 [0.06; 37.20] 3.69 [0.44; 30.96]	
Intervention = Olanzapi Beasley 1996b Davidson 2007 Egan 2013 Hirayasu 2010 Schmidt 2014 Shen 2014 Kane 2007b Marder 2007b Random effects model Heterogenetik: J ² = 0%, r ² =	ne 8 133 12 128 3 47 1 47 1 93 0 77 18 128 4 110 763 = 0, p = 0.50	1 68 10 123 1 83 0 138 3 101 0 78 13 127 3 110 828	+++++++++++++++++++++++++++++++++++++++	4.09 [0.52; 32.03] 1.15 [0.52; 2.57] 5.30 [0.57; 49.50] 8.75 [0.36; 211.10] 0.36 [0.04; 3.42] 1.37 [0.70; 2.68] 1.33 [0.31; 5.82] 1.42 [0.91; 2.22]	
Intervention = Paliperio Davidson 2007 Hirayasu 2010 Coppola 2011 Kane 2007b Marder 2007c Random effects model Heterogeneity: J ² = 0%, τ ²	done 12 125 1 136 2 70 68 375 12 224 930 = 0, p = 0.84	10 123 0 138 0 65 13 127 3 110 563	*	1.18 [0.53; 2.63] 3.04 [0.13; 74.07] 4.65 [0.23; 94.97] 1.77 [1.01; 3.10] 1.96 [0.57; 6.82] 1.65 [1.08; 2.51]	
Intervention = Perphen Chouinard 1975 Random effects model Heterogeneity: not applica	o 24 24 ble	1 24 24	-	0.33 [0.01; 7.79] 0.33 [0.01; 7.79]	
Intervention = Quetiapi Borison 1996 Small 1997 Fabre 1995 Lindenmayer 2008 Loebel 2013 Random effects model Heterogeneity: / ² = 20%, t	ine 3 54 7 96 3 8 27 267 11 120 545 ² = 0.1898, p = 0.	1 55 5 96 1 4 2 84 0 122 361 29	*	3.06 [0.33; 28.47] 1.40 [0.46; 4.26] 1.50 [0.22; 10.22] 4.25 [1.03; 17.49] - 23.38 [1.39; 392.36] 2.64 [1.13; 6.16]	
Intervention = Risperid Higuchi 2019b Marder 1994 Borison 1992 Geffen 2012 Potkin 2002 Liebermann 2015 Litiman 2016 Walling 2019 NCT00563706 Random effects model Heterogeneity: I ² = 52%, t	lone 1 65 3 64 0 53 9 91 15 99 9 82 1 31 1 37 2 43 565 $^2 = 1.2088, p = 0.$	0 133 0 66 0 54 11 93 1 103 1 85 3 55 0 74 0 37 700	* + + + + + + + + + + + + + + + + + + +	6.11 [0.25; 148.06] 7.22 [0.38; 136.97] 0.84 [0.36; 1.92] 15.61 [2.10; 115.93] 9.33 [1.21; 72.01] 0.59 [0.06; 5.44] 5.96 [0.25; 142.81] 4.31 [0.21; 86.99] 3.38 [1.11; 10.32]	
Clark 1971a Random effects model Heterogeneity: not applica	0 22 22 ble	0 21 21			
Intervention = Trifluopo Clark 1968b Random effects model Heterogeneity: not applica	erazine 1 18 18 ble	0 18 18		3.00 [0.13; 68.97] 3.00 [0.13; 68.97]	
Intervention = Ziprasid Daniel 1999 Study 115 2000 Cutler 2008 Keck 1998 Random effects model Heterogeneity: $I^2 = 0\%, \tau^2$	2 104 4 164 3 151 2 47 466 = 0, p = 0.76	2 92 1 83 1 152 0 48 375		0.88 [0.13; 6.15] 2.02 [0.23; 17.83] 3.02 [0.32; 28.71] 5.11 [0.25; 103.56] 1.93 [0.62; 5.96]	
Intervention = Zotepine Cooper 2000a Cooper 2000b Random effects model Heterogeneity: $J^2 = 0\%$, τ^2 Heterogeneity: $J^2 = 0\%$, τ^2	e 2 53 2 63 116 = 0, p = 0.61 = 0, p = 0.65	0 53 1 58 111 favo	0.01 0.1 1 10 100 rs intervention favors control	5.00 [0.25; 101.70] 1.84 [0.17; 19.77] 2.70 [0.42; 17.42]	

Figure 3. (Continued)

(C) study	Antipsy Events	chotic Total	Pla Events	acebo Total	Risk Ratio	RR	95%-CI
Amisulpride Carrière 2000 Haloperidol Costa e Silva 1989 Haloperidol Mortimer 2004 Olanzapine Random effects model Heterogenetty: /? = 0%, r? = 0, p = 0.42	0 5 1	94 20 189 303	2 3 0	105 20 188 313		0.22 1.67 2.98 1.36	[0.01; 4.59] [0.46; 6.06] [0.12; 72.79] [0.45; 4.14]
Aripiprazole Potkin 2003 Risperidone Random effects model Heterogeneity: not applicable	7	202 202	15	99 99	\$	0.23 0.23	[0.10; 0.54] [0.10; 0.54]
Chlorpromazine Clark 1971a Fluphenazine Clark 1971a Thioridazine	0	23	1	20	·	0.29	[0.01; 6.75]
Clark 1972 Loxapine Cooper 2000a Zotepine	9	19 53	9	18 53		0.95	[0.49; 1.84] [0.05; 5.35]
HGDV 2007 Olanzapine Kostakoglu 2001 Olanzapine	1 4	12	0	27 20		6.60	[0.29; 150.97] [0.39; 2.53]
Clark 1968b Trifluoperazine Rickels 1978 Tiotixene	6 1 15	100	6 1 5	101 18 39		1.01 1.00 2.92	[0.34; 3.03] [0.07; 14.79] [1.18; 7.27]
Leon 1974 Clozapine Li 2017 Quetiapine Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.50$	4	25 192 515	29	25 196 539	•	2.00 1.93 1.36	[0.40; 9.95] [0.88; 4.22] [0.96; 1.94]
Clozapine Kluge 2007 Olanzapine Leon 1974 Chiorpromazine Random effects model Heterogeneity: $I^2 = 0.296, r^2 = 2.2680, p = 0$	3 2	15 25 40	0 4	15 25 40		7.00 0.50 1.43	[0.39; 124.49] [0.10; 2.49] [0.11; 19.38]
Flupentixol Gattaz 2004 Olanzapine Random effects model Heterogeneity: not applicable	0	13 13	1	15 15		0.38 0.38	[0.02; 8.64] [0.02; 8.64]
Fluphenazine Clark 1971a Thioridazine Clark 1971a Chlorpromazine Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.98$	1	20 20 40	0	22 23 45		3.29 3.44 3.37	[0.14; 76.39] [0.15; 79.88] [0.36; 31.10]
Haloperidol A1281050 Ziprasidone Beasley 1996h Olanzanine	0	122	2	130		0.21	[0.01; 4.39]
Beasley 1997 Olanzapine Brook 2005 Ziprasidone	0	81 138	1 2	175		0.72	[0.03; 17.43] [0.14; 17.01]
Goff 1998 Ziprasidone Hwang 2001 Zotepine	0	17	0	20 35		1.00	[0.07; 15.36]
Min 1993 Risperidone Peuskens 1995 Risperidone	9	19 226	4	16 457	-	1.89	[0.72; 5.01] [0.51; 1.16]
Study 115 2000 Ziprasidone Borison 1992 Risperidone	2	85 53	40	164 53		0.96	[0.18; 5.16] [0.12; 72.00]
Murasaki 1993 Risperidone Protocol 128-301 1997 Ziprasidone	3 1 3	95 238	1	97 243		1.02	[0.27, 8.36] [0.06; 16.09] [0.17; 3.38]
Tollefson 1997 Olanzapine Haas 1982 Pimozide	3	660 15	17	1336 14		0.36	[0.11; 1.21]
Cassière 2000 Amisulpride Castière 2000 Amisulpride Costa e Silva 1989 Amisulpride Random effects model	23	105 20 2111	0	94 20 3545	 	4.48 0.60 0.80	[0.22; 92.11] [0.17; 2.18] [0.59; 1.09]
Iloperidone Cutter 2008 Ziprasidone Random effects model Heterogeneity: not applicable	28	303 303	3	151 151		4.65	[1.44; 15.05] [1.44; 15.05]
Loxapine Kiloh 1976_acute patients Trifluoperazi Kramer 1978 Thioridazine Clark 1972 Chloraromazine	ne 5 25	30 29	222	27 27		2.25	[0.48; 10.66] [0.84; 1.33]
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.57$ Lurasidone	-	77	-	73	è	1.07	[0.86; 1.33]
Loebel 2013 Quetapine Higuchi 2019b Risperidone Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.88$	7	246 262 508	11	120 65 185		0.31 0.25 0.30	[0.12; 0.78] [0.02; 3.91] [0.13; 0.73]
Molindone Itil 1971 Trifluoperazine Random effects model Heterogeneity: not applicable	3	30 30	3	30 30	-	1.00 1.00	[0.22; 4.56] [0.22; 4.56]
Olanzapine Davidson 2007 Paliperidone Gureje 2003 Risperidone	12	128 32	12	125 33		0.98	[0.46; 2.09] [0.01: 2.74]
Hirayasu 2010 Paliperidone Tran 1997 Risperidone	1	47	1	136 167		2.89	[0.18; 45.35] [0.15; 1.58]
Grootens 2009 Ziprasidone Kane 2007b Paliperidone	4 0 18	133 35 128	2 1 68	136 39 375		0.37	[0.38; 10.98] [0.02; 8.82] [0.48; 1.25]
Marder 2007c Paliperidone Beasley 1996b Haloperidol	4	110 133	12	224 69	- <u>+</u>	0.68	[0.22; 2.06] [0.53; 32.51]
HGDV 2007 Chlorpromazine Gattaz 2004 Flupentixol	0	27	1	12 13		0.15	[0.06; 33.83] [0.01; 3.47] [0.12; 58.96]
Kluge 2007 Clozapine Kostakoglu 2001 Chlorpromazine	0	15	3	15		0.14	[0.01; 2.54] [0.39; 2.53]
Tollefson 1997 Haloperidol Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.51$	17	1336 2694	3	660 2284		2.80 0.89	[0.61; 8.17] [0.82; 9.52] [0.66; 1.20]
Paliperidone Davidson 2007 Olanzapine	12	125	12	128	+	1.02	[0.48; 2.19]
Hirayasu 2010 Olanzapine Kane 2007b Olanzapine Marder 2007c Olanzapine	1 68 12	136 375 224	18 4	47 128 110		0.35 1.29 1.47	[0.02; 5.42] [0.80; 2.08] [0.49; 4.46]
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.76$ Perphenazine		860		413	Ĩ	1.21	[0.83; 1.76]
Hoyberg 1993 Risperidone Random effects model Heterogeneity: not applicable	5	52	10	55		0.53 0.53	[0.19; 1.44] [0.19; 1.44]
Haas 1982 Haloperidol Random effects model Heterogeneity: not applicable	0	14 14	0	15 15			
Li 2017 Chlorpromazine Peuskens 1997 Chlorpromazine Loebel 2013 Lurasidone Random effects model Heterogeneits: /? = 77%, t² = 0.7570, p = 0	9 6 11	196 101 120 417	17 6 7	192 100 246 538	*	0.52 0.99 3.22 1.17	[0.24; 1.13] [0.33; 2.97] [1.28; 8.10] [0.38; 3.59]
Risperidone A1281046 Ziprasidone Addington 2004 Ziprasidone	1	29	1	29		1.00	[0.07; 15.24]
Zhang 2011 Ziprasidone Higuchi 2019b Lurasidone	2	121 65	6	118		0.33	[0.07; 1.58] [0.26; 63.59]
Gureje 2003 Olanzapine Marder 1994 Haloperidol Min 1993 Haloperidol	3	33 64 16	0	32 66		6.79 3.09	[0.36; 126.37] [0.33; 28.97] [0.20: 1.40]
Peuskens 1995 Haloperidol Tran 1997 Olanzapine	71	457 167	27 4	226 172		1.30	[0.86; 1.97] [0.63; 6.71]
Borison 1992 Haloperidol Ceskova 1993 Haloperidol Hovberg 1993 Perphenazine	2	53 31 55	1 3 5	53 52		0.33 0.67 1.89	[0.01; 8.00] [0.12; 3.72] [0.69: 5.16]
Murasaki 1993 Haloperidol Potkin 2003 Aripiprazole Random effects model	1 15	97 99 1434	17	95 202 1506		0.98 4.37 1.35	[0.06; 15.43] [1.84; 10.38] [0.87; 2.10]
Heterogeneity: <i>P</i> = 32%, <i>T</i> = 0.1839, <i>p</i> = 0 Sulpiride Cassano 1975 Haloperidol Random effects model Meterogeneits out applicable	1	34 34	o	36 36		3.17 3.17	[0.13; 75.31] [0.13; 75.31]
Thioridazine Clark 1971a Chlorpromazine Clark 1971a Eluphenazine	0	22	0	23		0.30	10.01: 7.051
Kramer 1978 Loxapine Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.44$	22	27	25	29 72	4	0.95 0.94	[0.75; 1.19] [0.75; 1.18]
Saral 1987 Zotepine Rickels 1978 Chlorpromazine Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.39$	0 5	46 39 85	5 15	48 40 88	*	0.09 0.34 0.30	[0.01; 1.67] [0.14; 0.85] [0.13; 0.72]
Triffuoperazine Itil 1971 Molindone Clark 1968b Chlorpromazine Kiloh 1976, acute patients Loxapine Random effects model Heterometer d ² = 0, p = 0.74	3 1 2	30 18 27 75	3 1 5	30 18 30 78		1.00 1.00 0.44 0.71	[0.22; 4.56] [0.07; 14.79] [0.09; 2.10] [0.26; 1.95]
Ziprasidone							10.07
A1281040 Risperidone A1281050 Haloperidol Brook 2005 Haloperidol	1 2 2	29 130 429	1 0 1	29 122 138		1.00 4.69 0.64	[0.07; 15.24] [0.23; 96.79] [0.06; 7.04]
Goff 1998 Haloperidol Study 115 2000 Haloperidol	04	20 164	0	17 85		1.04	[0.19; 5.55]
Simpson 2004 Olanzapine Cutler 2008 lloperidone	4 2 3	149 136 151	3 4 28	133 303		0.49	[0.09; 2.62] [0.07; 0.70]
Grootens 2009 Olanzapine Protocol 128-301 1997 Haloperidol Zhang 2011 Biangridone	1 4	39 243	0 3	35 238		2.70	[0.11; 64.08] [0.30; 5.77]
Random effects model Heterogeneity: $I^2 = 17\%$, $\tau^2 = 0.1739$, $p = 0$	6 0.28	118 1608	2	1368	-	3.08 0.92	[0.49; 1.72]
Zotepine Cooper 2000a Chlorpromazine	2	53	1	53		2.00	[0.19; 21.40]
Sarai 1987 Tiotixene Random effects model	1	35 48 136	0	35 46 134		- 10.55 2.57	[0.60; 185.45] [0.56; 11.75]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.46$ Heterogeneity: $I^2 = 23\%$, $\tau^2 = 0.0817$, $p = 0$	0.02				0.01 0.1 1 10 100	D	

Figure 3. (Continued)



Risk of bias

The percentage of studies with low/unclear/high risk of bias for the individual items was randomization (57.1%, 42.9%, 0%), allocation (42.93%, 57.1%, 0%), blinding of patients and personnel (57.1%, 36.4%, 6.5%), rater blinding (59.7%, 32.54%, 7.8%), missing outcomes (67.5%, 20.8%, 11.7%), selective reporting (72.7%, 10.4%, 16.9%) and other bias (89.6%, 5.2%, 5.2%), whereas selective reporting was based on overall symptom scales like positive and negative syndrome scale (Supplemental Appendix 5).

Assessment of heterogeneity

We found no significant heterogeneity for any comparison concerning the outcome bradycardia. Concerning tachycardia, only the comparison of risperidone with placebo ($\tau^2 = 1.2088, p = 0.04$; I² = 52%) and quetiapine with other antipsychotics ($\tau^2 = 0.7570, p = 0.01$; I² = 77%) revealed significant heterogeneity. Many comparisons consisted only of one study, so heterogeneity assessment was not applicable.

Sensitivity analysis

Using a fixed-effects model instead of a randomeffects model in a sensitivity analysis changed the results only in case of tachycardia. Chlorpromazine compared with any antipsychotic using a fixedeffects model was statistically significant and RR raised from 1.36 (95% CI = 0.96-1.94, p = 0.025) to 1.46 (95% CI = 1.03-2.08, p = 0.003). Results for all other comparisons did not change materially. We did not conduct the *a priori* planned sensitivity analysis *exclusion of open studies* as there were only two open studies in the complete data set. Exclusion of long-term studies (duration > 13 weeks) did not change the results for bradycardia or tachycardia (Supplemental Appendix 7).

Publication bias

We did not assess small study bias for bradycardia events as no comparison had 10 or more studies. We did a contour-enhanced funnel plots for tachycardia events, which revealed a possibility that small trials with a lower relative risk for tachycardia events in the antipsychotic group could be missing (Figure 4).

Discussion

The analysis presents bradycardia and tachycardia events from 77 studies with 16,907 participants



Favours antipsychotic Favours placebo

Figure 4. Contour-enhanced funnel plot for all antipsychotics compared with placebo.

Risk of tachycardia events of all antipsychotics compared with placebo. Circles represent effect sizes of individual studies measured as risk ratio. Missing studies were estimated using the trim-and-fill method. Original effect sizes are represented by empty circles and estimated ones by filled circles.

using antipsychotics for the treatment of acute schizophrenia. Based on few data, we found significant differences in bradycardia events neither between antipsychotics and placebo nor between individual antipsychotics. Overall bradycardia is primarily dangerous for people at risk, for example, after a myocardial infarction or with already existing arrhythmia (e.g. branch blocks).²² In contrast, bradycardia can be even physiological in young or exercised people.²³ Nevertheless, bradycardias can cause dizziness and are responsible for 3–10% of syncopes.²⁴

The risk for tachycardia events was 1.81 times higher for antipsychotics compared with placebo with a number needed to harm of 43. There are some substances that have a significantly higher risk for tachycardia than placebo. Some of the reported tachycardias may be reflex tachycardias caused by an adequate autonomic reflex to orthostatic hypotension. Undermining this hypothesis is the fact that antipsychotics with a higher risk for orthostatic hypotension like iloperidone and chlorpromazine have a higher risk for tachycardias.²⁵ The antipsychotic substance most often associated with tachycardia is clozapine.²⁶ This may be related to the vagolytic effects of clozapine. Unfortunately, we did not find an RCT that compared clozapine with placebo, only one comparison with olanzapine²⁷ and one with chlorpromazine.²⁸ Neither found significant differences in tachycardia risks. Haloperidol that can be associated with prolongation of the QT_C interval, especially when given intravenously,²⁹ had a significantly lower risk of tachycardia compared with olanzapine based on three studies with 2454 participants (RR = 0.35, p = 0.04).

We conducted the analysis using state-of-the-art methods and following the PRISMA guidelines. Nevertheless, there are some limitations. The primary outcome of most included studies was efficacy of antipsychotics. So bradycardia and tachycardia events were only reported as adverse events. It is unclear whether changes in heart rate did not occur in most of the studies or whether the studies did not report these events. No study presented a bradycardia or tachycardia definition in beats per minute, so we had to rely on the original author's definition of these events. Of the 469 studies examining acute treatment with antipsychotics, only 77 studies with 15,732 participants reported data for tachycardia events and even less for bradycardia events (17 studies with 6866 participants). Bradycardias and tachycardias could be missed as the heart rate of patients is not monitored 24 h. This could lead to an underestimation of the 'real' event rate. We did not analyse mean heart rate, which would be interesting and allow to test for factors that could mitigate changes in heart rate like weight gain. Unfortunately, authors often did not state whether they counted all bradycardias and tachycardias irrespectively if the underlying rhythm was sinus rhythm or not. So tachycardia in the presence of atrial fibrillation could be counted even it is most likely not caused by the intake of antipsychotic drugs. We also did not analyse other arrhythmias, except QTc prolongation which is published elsewhere,² because they are even rarer than bradycardias. To pool the results, we needed a homogeneous sample. Therefore, we had to exclude studies focused on elderly patients, although bradycardias and tachvcardias are more dangerous for this population,³⁰ but only few studies were excluded on this basis.³¹ So the generalizability of our results is limited, especially as patients with concomitant somatic medial illness are typically excluded

from randomized controlled trials of antipsychotics in schizophrenia. The risk-of-bias assessment was focused on overall efficacy measures, but only the risk-of-bias items 'missing outcomes' and 'selective reporting' are not outcome-specific.

Conclusion

There is evidence that treatment with antipsychotics increases the risk for tachycardia. Therefore, especially patients with risk factors should undergo electrocardiography and be monitored closely during antipsychotic treatment.³² In case of preexisting cardiovascular disease, an antipsychotic agent with low risk profile should be used.

Ethics approval and consent to participate Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Maximilian Huhn: Conceptualization; Data curation; Formal analysis; Methodology; Validation; Writing – original draft; Writing – review & editing.

Thomas Arndt: Data curation; Formal analysis; Investigation; Writing – review & editing.

Johannes Schneider-Thoma: Data curation; Formal analysis; Writing – original draft.

Stefan Leucht: Conceptualization; Funding acquisition; Project administration; Supervision; Validation; Writing – original draft.

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Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: MH has received honoraria as a consultant for Recordati. In the past 3 years, SL has received honoraria as a consultant/advisor and/or for lectures from Angelini, Boehringer Ingelheim, Gedeon Richter, Janssen, Johnson & Johnson, Lundbeck, LTS Lohmann, MSD, Otsuka, Recordati, SanofiAventis, Sandoz, Sunovion, TEVA, Eisai, Rovi, Medichem and Mitsubishi. All other authors declare no competing interests.

Availability of data and materials

Not applicable.

Supplemental material

Supplemental material for this article is available online.

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