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ANTIPSYCHOTICS IN THE TREATMENT OF BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS IN DEMENTIA. A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS.

ANTIPSYCHOTISCHE THERAPIE VON VERHALTENS- UND PSYCHISCHEN STÖRUNGEN BEI DEMENZ. EINE SYSTEMATISCHE ÜBERSICHTSARBEIT UND META-ANALYSE RANDOMISIERTER, KONTROLLIERTER STUDIEN.

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LIST OF ABBREVIATIONS

5HT-2	Serotonine-2
AChEI	Acetylcholine Esterase Inhibitor
AD	Alzheimer's Dementia
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive subscale
AI	AccidentalInjury
APP	Amyloid Precursor Protein
Aβ	Beta-Amyloid
BEHAVE AD	Behavioural pathology in Alzheimer's disease Rating Scale
BPRS	Brief Psychiatric Rating Scale
BPSD	Behavioural and Psychological Symptoms of Dementia
CI	Confidence Interval
CMAI	Cohen Mansfield Agitation Inventory
CVAE	Cerebrovascular Adverse Events
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DO	Drop-Outs
DOAE	Drop-Outs due to Adverse Events
DOI	Drop-Outs due to Inefficacy
EFNS	European Federation of Neurological Societies
EPS	Extrapyramidal Symptoms
FDA	Food and Drug Administration

FGA	First Generation Antipsychotics
GCP	Good Clinical Practice
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LOCF	Last Observation Carried Forward
MMSE	Mini Mental State Examination
NPI	Neuropsychiatric Inventory
OR	Odds Ratio
RCT	Randomised Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Events
SD	Standard Deviation
SGA	Second Generation Antipsychotics
SMD	Standardized Mean Differences
VD	Vascular Dementia

ABSTRACT

ENGLISH

Objective. Behavioural and psychological symptoms in dementia (BPSD) are common and are often treated with antipsychotics. Efficacy seems to be low and side effects are considerable. One potential side-effect might be cognitive decline. Further, there has however not been made an attempt to distinguish first and second generation antipsychotics in terms of efficacy and tolerability in these patients so far.

Method. The databases PsiTri, Medline, Scopus, Embase, EBMR and www.ClincalStudyResults.org were searched for randomized, placebo-controlled trials using antipsychotics for treating BPSD and evaluated cognitive decline, efficacy, effectiveness and tolerability. Their results were summarized in a comprehensive meta-analysis.

Results. After application of exclusion criteria, 29 studies were eligible for inclusion to the meta-analysis, ten of whom provided also data on cognitive functioning. Following pooled meta-analytic efficacy calculations both, conventional and atypical antipsychotics proved to be effective in treating BPSD as compared to placebo; effect-sizes, however, were very low; first generation antipsychotics showed a somewhat higher, yet still low effect-size. In terms of effectiveness and tolerability no difference was found. Treatment with antipsychotics as compared to placebo may lead to cognitive decline.

Conclusions. Despite widespread clinical use the efficacy of antipsychotics in treating BPSD is low and is accompanied by considerable side-effects. Following randomised, controlled trials, the benefit-risk ratio is low with no relevant difference between first and second generation antipsychotics.

GERMAN

Fragestellung. Verhaltensstörungen und psychische Störungen bei Demenzerkrankung sind häufig und werden oftmals mit Antipsychotika behandelt. Deren Wirksamkeit scheint gering zu sein, wobei Nebenwirkungen beträchtlich sind. Eine mögliche Nebenwirkung könnte die Abnahme der kognitiven Leistungsfähigkeit sein. Darüber hinaus wurden Antipsychotika der ersten und zweiten Generation hinsichtlich deren Wirksamkeit und Verträglichkeit bisher nicht differenziert.

Methoden. Die Datenbanken PsiTri, Medline, Scopus, Embase, EBMR und www.ClinicalStudyResults.org wurden nach randomisierten, Placebo-kontrollierten Studien durchsucht, in denen BPSD mit Antipsychotika therapiert wurde. Es wurden kognitiver Verfall, Wirksamkeit, Effektivität und Verträglichkeit ausgewertet. Deren Ergebnisse wurden in einer zusammenfassenden Meta-Analyse berechnet.

Ergebnisse. Nach Anwendung der Ausschlusskriterien konnten 29 Studien in die Meta-Analyse eingeschlossen werden, von denen zehn Studien Daten zur kognitiven Funktion lieferten. Nach den zusammengefassten meta-analytischen Berechnungen stellten sich beide, konventionelle und atypische Antipsychotika, im Vergleich zu Placebo als wirksam heraus. Die Effektstärke war sehr gering. Antipsychotika der ersten Generation zeigten einen etwas höhere Effektstärke, die aber immer noch als niedrig zu bewerten ist. Hinsichtlich Effektivität und Verträglichkeit fand sich kein Unterschied. Die Behandlung mit Antipsychotika könnte im Vergleich zu Placebo zu einer Abnahme der Kognition führen.

Folgerung. Trotz weit verbreiteter klinischer Anwendung ist die Wirksamkeit von Antipsychotika bei der Behandlung von BPSD gering und von nennenswerten Nebenwirkungen begleitet. Aus den randomisierten, kontrollierten Studien geht ein geringes Nutzen-Risiko-Verhältnis hervor, bei dem es keine relevanten Unterschiede zwischen Antipsychotika der ersten und zweiten Generation gibt.

INTRODUCTION

Behavioural and psychological symptoms of dementia (BPSD) affect nearly all patients suffering from dementia [1]. Neil found that BPSD were present in 96.2% in their collective of demented patients [2]. The most severe symptoms caregivers and physicians have to cope with, are depression, anxiety, sleeplessness, hallucinations, delusions, misidentifications, physical aggression, restlessness and wandering [3]. Thus, treatment of BPSD faces more than one problem: the pathology of the patient and the burden to the caregivers with all their consequences. Matsumoto found that "the burden associated with BPSD is different for each symptom and does not always depend on frequency and severity of BPSD". These findings suggest that some symptoms, such as agitation, aggression, irritability or lability may affect the caregivers significantly, although their frequency and severity are low [4]. There is still no efficient treatment strategy with convincing evidence for patients suffering from BPSD, neither with behavioural nor pharmacological approaches. Concerning pharmacological treatment there is no sufficient evidence for the use of antidepressants, mood-stabilisers or benzodiazepines. Anti-dementive agents such as choline-esterase inhibitors or memantine may have an effect on BPSD in certain subgroups. In clinical practice, antipsychotics are most commonly used for the treatment of these symptoms. Some meta-analyses have been conducted previously to evaluate their efficacy. Efficacy of antipsychotic treatment, despite being significant, seems to be of very low effect size [5, 6] and side-effects are considerable [7-11]. In the light of the controversial discussion on the benefits of second generation antipsychotics (SGA) over first generation antipsychotics (FGA) in patients with schizophrenia or bipolar disorder it also seems necessary to look at potential differences between these two groups in patients with dementia.

Furthermore, some few studies indicate that the use of antipsychotic medication may have malevolent effects on cognitive functioning. In a two year prospective, longitudinal study it was found that patients with dementia taking antipsychotics had a cognitive decline twice as fast as patients who did not one year after first prescription [12]. A significant cognitive decline subsequent to the use of

antipsychotics for treating BPSD in patients with dementia would seriously limit their use. Taking into account that the efficacy of antipsychotics for BPSD is doubtful, the cost-effectiveness ratio of antipsychotics in patients with dementia would need to be reassessed.

Therefore, the aim of this review and meta-analysis was to elucidate whether the use of antipsychotics in patients with dementia goes along with accelerated cognitive decline and to update the data on efficacy and tolerability of antipsychotics with the recently published studies (e.g. CATIE-AD) and to compare efficacy, effectiveness and tolerability of SGA versus FGA.

METHODS

DATA ACQUISITION

All published and unpublished randomized controlled trials that assessed the efficacy and tolerability of antipsychotics in the treatment of BPSD were searched for in PsiTri (http://psitri.stakes.fi). PSITRI is a register of controlled trials that compiles the registers of all Cochrane review groups in the field of mental health. The registers of the single Cochrane review groups are compiled by regular searches of numerous electronic databases and conference abstract books and hand searching of major journals (the exact search strategies of the individual review groups are listed in the Cochrane Library). Furthermore MEDLINE, EMBASE, SCOPUS and EBMR (last update: December 2008) were searched.

The abstracts, titles, and index terms of studies were searched using the following key words: antipsychotic, antipsychotics, neuroleptic, neuroleptics, haloperidol, quetiapine, risperidone, aripiprazole, clozapine, olanzapine, zuclopenthixole, chlorpromazine, thioridazine, flupenthixol, sulpiride, melperone, pipamperone, pimozide and ziprasidone in conjunction with dementia, Alzheimer, Alzheimer's, AD, vascular dementia, BPSD, behavioural and psychological, Pick, Pick's Disease.

ClinicalStudyResults (http://ClinicalStudyResults.org), an open database for trials, was also searched for diagnosis dementia or Alzheimer dementia in conjunction with quetiapine, risperidone, aripiprazole and olanzapine (last update: December 2008).

In addition, the reference sections of included articles and key reviews were screened, and the first or last authors of the included studies and pharmaceutical companies (AstraZeneca, EliLilly, Janssen-Cilag, Bristol-Myers Squib, Pfizer) were asked by e-mail between December 2005 and October 2007 whether they were aware of further trials. They were also contacted for the provision of missing data necessary for the meta-analysis. We are grateful to Herz et al., DeVane et al., Luggen et al., Schneider et al., Nygaard et al. and Kasckow et al. for sending us additional data. In case clinical study reports (CSR) and published papers of the same study were both available, we referenced the CSR because it usually included

more data for evaluation. Two raters (F.G.P. and A.W.) independently screened the identified references.

A rating based on the 3 quality categories described in the Cochrane Collaboration Handbook was given for each trial; A: low risk of bias (adequate allocation concealment), B: moderate risk of bias (some doubt about the results, mainly studies said to be randomised, but without an explanation of the method), and C: high risk of bias (clearly inadequate allocation concealment, e.g. alternate randomisation) [13]. The inclusion criterion for this review was a low or moderate risk of bias (category A or B, respectively).

All papers were rated and data extracted independently by F.G.P. and A.W. onto standard simple forms. Any disagreement was discussed with a third reviewer (S.L.), and decisions were documented. If necessary, authors of studies were contacted for clarification.

Inclusion criteria were at least single-blinded, randomized, controlled trials with minimum duration of one week which provide the data in one or more of the following categories:

1. Efficacy for behavioural symptoms: Mean Endpoint or Mean Change in at least one of the following scales (in order of importance):
    - Cohen Mansfield Agitation Inventory (CMAI)
    - Neuropsychiatric Inventory (NPI)
    - Brief Psychiatric Rating Scale (BPRS)
    - Behavioural pathology in Alzheimer's disease Rating Scale (BEHAVE AD)
    - Agitation Analog Scale
    - Neurobehavioral Rating Scale
2. Acceptability of treatment and effectiveness:
    - Drop-Out rate overall
    - Drop-Outs due to Adverse Events (DOAE)
    - Drop-Outs due to Inefficacy (DOI)
3. Tolerability: Data on occurring of
    - extrapyramidal symptoms (EPS)

- death
- serious adverse events (SAE)
- somnolence
- agitation
- accidental injury
- akathisia
- dyskinesia
- parkinsonoid

4. Cognition: Mean Endpoint or Mean Change in cognitive scales; only the Mini Mental State Examination (MMSE) was applied in all studies investigating cognitive functioning.

OUTCOME PARAMETERS

The primary outcome of interest was the mean change in efficacy as rated with the above named instruments from baseline to endpoint. Further outcome parameters were the rate of response and acceptability/effectiveness criteria such as the number of participants leaving the study early (Drop-Outs) for any reason, DOAE, DOI and tolerability issues including cognitive decline.

In a 'once randomized – analyzed' approach (Last Observed Carrier Forward method) we assumed in the case of dichotomous data that participants who dropped out prior to completion had no change in their condition unless otherwise stated. Continuous data had to be reported as presented in the original studies without any assumptions about those lost to follow-up, but intent-to-treat results were used whenever presented.

META-ANALYTIC CALCULATIONS

The outcome data were combined in a meta-analysis. The standardized mean differences (SMD) based on Hedges's adjusted g (a slightly modified version of the Cohen's D for correction in the case of small participant numbers below 10) was

calculated [14] and their 95% confidence interval (CI) as effect size measures. When standard deviations were not indicated, they were either derived from *P* values or the mean standard deviations of the other studies was used.

For dichotomous data, the relative risk (RR) along with its 95% confidence interval (CI) was estimated. The RR is defined as the ratio of the risk of an unfavourable outcome among treatment-allocated participants to the corresponding risk of an unfavourable outcome among those in the control group.

Whereas many meta-analysts preferred to use odds ratios some years ago, it has been shown that the RR is more intuitive [15] and that odds ratios tend to be interpreted as RR by clinicians [16]. This misinterpretation then leads to an overestimated impression of the effect. We also present absolute risk differences and numbers-needed-to-treat/harm calculated as the inverse of the absolute difference.

There are disadvantages of both fixed and random effects models. The random effects model takes heterogeneity among studies into account, even if this heterogeneity is not statistically significant, but gives more weight to smaller studies which are often most prone to bias. Therefore, results based on both the random effects model (primary model) and the fixed effects model are presented [17]. Study heterogeneity was assessed by a chi-square test and the I-square statistic [18]. The chi-square test contrasts the effect sizes of the individual trials with the pooled effect size. Significance levels of $p < 0.1$ were set *a priori* in order to assume the presence of heterogeneity. The I-square statistic provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. We interpreted values ≥ 50% as considerable heterogeneity [18]. When the results were statistically significantly heterogeneous, reasons for the heterogeneity were sought for by re-reading the publications.

Studies with negative results are less likely to be published than studies with significant results. The possibility of such publication bias was examined using the "funnel plot" method described by Egger and colleagues [19].

All calculations were performed using Comprehensive Meta-analysis version 2. The exact formulas are reported there [20]. $P < 0,05$ was considered statistically significant.

RESULTS

INCLUDED STUDIES

The search yielded 376 publications. 100 studies were more closely inspected of which 71 were excluded for the reasons specified in figure 1. 29 trials with 37 active comparator arms and 6.482 participants (antipsychotics: 4.288; placebo: 2.194) were included and of these 26 provided data on either efficacy [21-46] 26 on effectiveness [21-33, 35-42, 44, 46-49], 19 on tolerability [22-24, 26-33, 37, 39, 40, 42, 44, 46, 47, 49], and 10 on cognitive functioning [21-24, 31, 42-46] (see table 1, for further details see table 2). Studies with the following drugs were identified: aripiprazole, olanzapine, quetiapine, risperidone (SGA), and haloperidol, loxapine, perphenazine, pimozide, thioridazine, thiothixene, tiapride (FGA).

All but three studies were short-term and lasted 12 weeks or less. Therefore, these results were used in the primary analysis. We assessed in a sensitivity analysis whether the results changed when long-term (26 weeks) instead of short-term results were used [24, 26], and one 16 weeks study was added [45]. In the tolerability and the effectiveness analysis we only used data from long-term assessment. In the cognitive analysis all but two studies were short-term and lasted 12 weeks or less. Therefore, these results were used in the primary analysis. We assessed in a sensitivity analysis whether the results changed when long-terms (26 weeks) instead of short-term results were used [24], and one 16 weeks study was added [45].

FIGURE 1: SELECTION OF STUDIES TO BE INCLUDED IN META-ANALYTIC CALCULATION

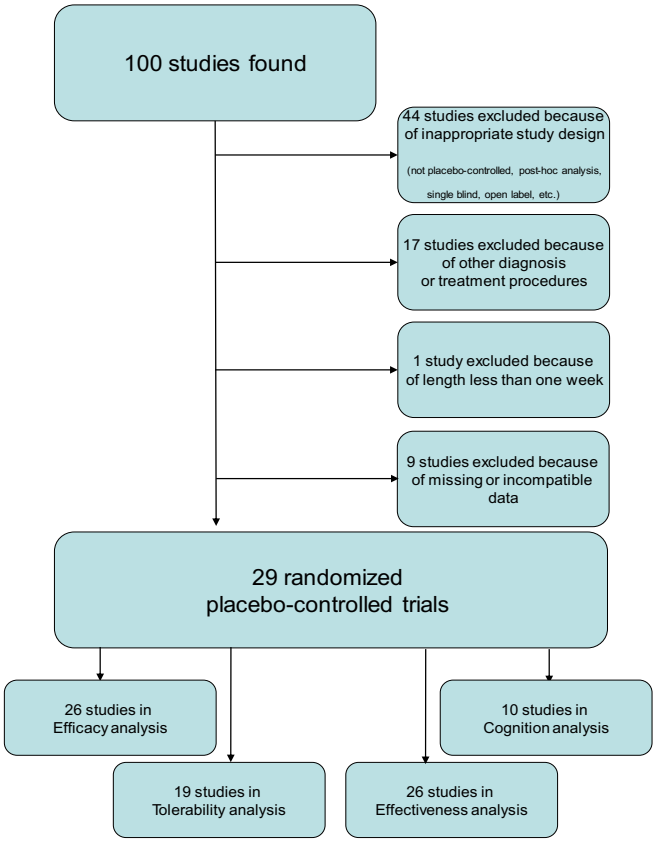


TABLE 1: TOTAL NUMBER OF PATIENTS OF INCLUDED TRIALS FOR EFFICACY, ACCEPTABILITY/EFFECTIVENESS AND TOLERABILITY ANALYSIS

Study participants in the treatment arm with the following agent	N Antipsychotic	N Placebo	N trials
Aripiprazole	597	354	3
Olanzapine	1.288	628	7
Quetiapine	477	384	5
Risperidone	1.288	948	8
SGA	3.650	1.928	
Haloperidol	414	402	7
Loxapine	38	39	2
Perphenazine	33	21	1
Pimozide	18	23	1
Thioridazine	17	17	1
Thiothixene	16	16	1
Tiapride	102	103	1
FGA	638	479	
Overall	4.288	2.194	

The number of patients receiving placebo in the SGA and FGA comparisons does not add up to the overall number because of multiple arms in some studies.

TABLE 2: OVERVIEW OF ALL INCLUDED TRIALS

Study	Intervention	Dose in mg (mean dose)	Diagnosis	MMSE Mean at Baseline (SD)	Duration (weeks)	Mean Age in Years (SD)	Female (%)	Efficacy Score	Available Data on													N rand	N LOCF	C (%)
									Dyskinesia	Akathasia	Parkinsonism	EPS	Death	Agitation	SAE	Somnolence	Accidental Injuries	DO global	DO Inefficacy	DO Adverse Events	Cognitive course			
CN138005 2004	**Aripirazole**	2-15	AD	13,26	10	N / A	76	CMAI					x		x					x	x	125	126	N / A
	Placebo			13,94		N / A																131	121	N / A
Breder 2004	**Aripirazole**	2-10	AD	12,4 (4.4)	10	82.5	79	CMAI				x	x	x		x	x	x	x	x		366	347	N / A
	Placebo																					121	115	N / A
De Deyn 2005	**Aripirazole**	2-15	AD	14,13	10	81,5	72	NPI				x	x		x			x	x	x	x	106	103	83
	Placebo			14,35																		102	100	82
Herz unpublished	**Olanzapine**	2,5-20	AD	N / A	6	N / A	N / A	Agita-tion Analog										x	x	x		7	4	N / A
	Placebo			N / A		N / A	N / A															8	8	N / A
F1D-MC-HGAO 2005	**Olanzapine**	1-8	AD	11,08 (7,33)	8	78,24 (6,91)	65,8	BEHAVE AD		x	x			x		x		x	x	x	x	120	100	51,7
	Placebo			10,25 (6,30)		78,93 (6,3)	66,9															118	105	51,7
Street 2000	**Olanzapine**	5-15	AD	6,8 (6,6)	6	83,15 (6,57)	61,0	NPI		x	x		x	x	x	x	x	x	x	x	x	159	156	73,0
	Placebo			7,3 (6,3)		81,4 (6,7)	61,7															47	44	76,6
Deberdt 2005	**Olanzapine**	2,5-10 (5,2)	AD, VD, mixed	14,0 (5,4)	12	77,9 (7,7)	69,1	NPI		x	x		x	x		x	x	x		x		204	193	62,3
	Placebo			15,2 (6,2)		79,8 (7,2)	63,8															94	91	79,8
F1D-MC-HGIC 2005	**Olanzapine**	2,5-5	AD	21,49	12	77,57 (8,03)	55,1	NPI													x	178	171	N / A
* short term	Placebo			21,47		77,72 (7,78)	57,8															90	88	N / A
F1D-MC-HGIC 2005	**Olanzapine**	2,5-5	AD	21,49	26	77,57 (8,03)	55,1	NPI	x	x	x					x	x	x	x	x	x	178	171	60,1
* long term	Placebo			21,47		77,72 (7,78)	57,8															90	88	73,3
De Deyn 2004	**Olanzapine**	1-7,5	AD	N / A	10	76,6 (10,4)	75	CGI	x		x		x	x	x			x	x	x		520	513	N / A
F1D-MC-HGIV	Placebo			N / A																		129	129	N / A
Sultzer 2008	**Olanzapine**	(5,5)	NPI	15,0 (5,4)	12	77,9 (7,5)	56	NPI													x	100	99	20,0
	Placebo			14,7 (5,8)																		142	139	14,8
Schneider 2006	**Olanzapine**	(5,5)	AD	15,0 (5,4)	12	78,8 (7,3)	55		x	x	x	x	x	x	x	x	x	x	x	x		100	40	20,0
	Placebo			14,7 (5,8)		77,3 (7,1)	57															142	47	14,8
Tariot 2006	**Quetiapine**	(96,9)	AD	12,40 (5,09)	10	81,92 (6,85)	72,5	BPRS					x	x	x	x	x	x	x	x	x	91	85	68,1
	Placebo			13,15 (5,44)		83,93 (6,66)	79,8															99	94	63,6
Ballard 2005	**Quetiapine**	2 x 25-50	AD	N / A	6	84,2 (8,6)	87,1	CMAI					x					x				31	27	74
* short term	Placebo			N / A		83,0 (6,8)	77,4															31	29	96,8
Ballard 2005	**Quetiapine**	2 x 50	AD	N / A	26	84,2 (8,6)	87,1	CMAI														31	27	N / A
* long term	Placebo			N / A		83,0 (6,8)	77,4															31	30	N / A
Zhong 2007	**Quetiapine**	100-200	AD, VD	5,2 (3,8)	10	83,2 (7,6)	75,5	CMAI				x	x		x	x		x	x	x	x	241	234	64,3
	Placebo			5,5 (4,0)		83,2 (7,2)	70,7															92	92	65,2
Sultzer 2008	Quetiapine	(56,5)	AD	14,9 (6,1)	12	77,9 (7,5)	56	NPI													x	94	94	18,1
	Placebo			14,7 (5,8)																		142	139	14,8
Schneider 2006	**Quetiapine**	(56,5)	AD	14,9 (6,1)	12	77,3 (8,7)	53		x	x	x	x	x	x	x	x	x	x	x	x		94	31	18,1
	Placebo			14,7 (5,8)		77,3 (7,1)	57															142	47	14,8
Paleacu 2007	**Quetiapine**	25-300	AD	14,5 (6,3)	6	82,2 (6,4)	65			x	x							x	x	x		20	20	60
	Placebo			14,3 (6,8)																		20	20	75
Herz unpublished	**Risperidone**	0,5 – 4	AD	N / A	6	N / A	N / A	Agitation Analog										x	x	x		14	13	N / A
	Placebo			N / A		N / A	N / A															8	8	N / A
Brodaty 2003	**Risperidone**	(0,95)	AD, VD, mixed	5,14 (SE 0,45)	12	83,2 (SE 0,51)	71,2	BEHAVE AD				x	x	x	x	x	x	x	x	x		167	149	73,1
	Placebo			5,78 (SE 0,46)		82,7 (SE 0,64)	72,4															170	152	67,1

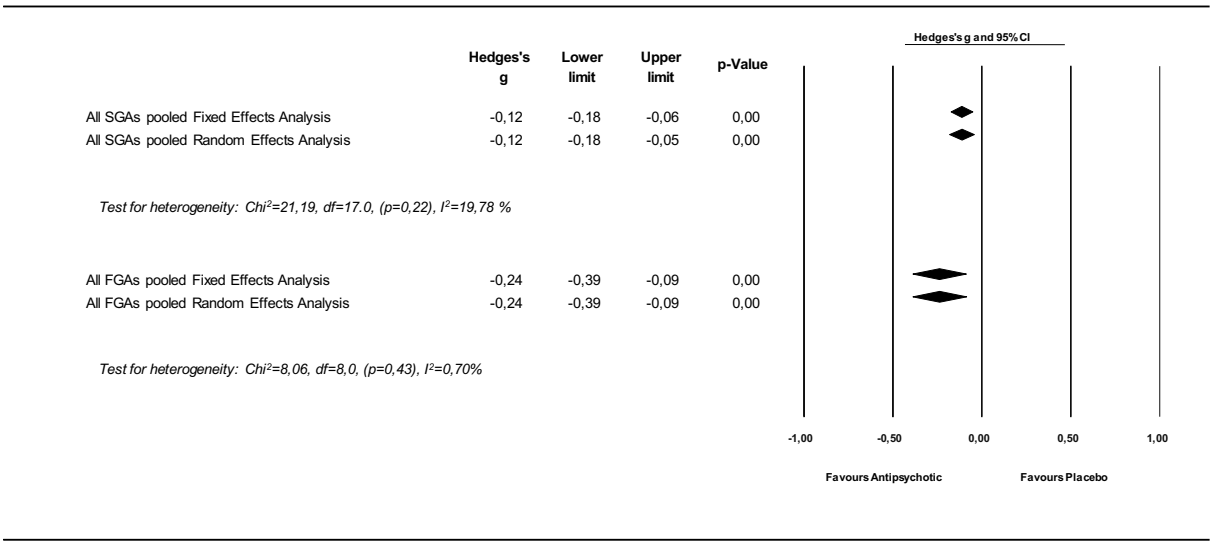
De Deyn 1999	**Risperidone**	(1,1)	AD, VD, mixed	8,6	12	medi an 81	56,5	BEHAVE AD								x		x				115	115	59,1
	Placebo			8,8		medi an 81	58,8															114	114	64,9
Katz 1999	**Risperidone**	0,5-2	AD, VD, mixed	6,6 (6,3)	12	82,7 (7,7)	67,8	BEHAVE AD				x	x	x	x	x	x	x	x	x		456	456	68,4
	Placebo																					163	161	73,0
Mintzer 2006	**Risperidone**	1-1,5	AD	13,2 (4,93)	8	83,4 (7,20)	77,9	BEHAVE AD					x	x	x	x	x	x	x	x		235	201	75
	Placebo			13,2 (5,01)		83,2 (7,38)	76,1															238	212	75
RIS-BEL 14 2001	**Risperidone**	1-4	AD	9,8	4	79,0	65	BEHAVE AD										x	x	x	x	20	20	80
	Placebo			7,8		77,6	74															19	19	78,9
Deberdt 2005	**Risperidone**	0,5-2 (1,0)	AD, VD, mixed	14,7 (5,5)	10	78,0 (6,9)	62,8	NPI	x	x	x		x	x		x	x			x		196	190	68,9
	Placebo			15,2 (6,2)		79,8 (7,2)	63,8															94	91	79,8
Sultzer 2008	Risperidone	(1,0)	NPI	15,7 (6,1)	12	77,9 (7,5)	56	NPI													x	85	84	22,4
	Placebo			14,7 (5,8)																		142	139	14,8
Schneider 2006	**Risperidone**	(1,0)	AD	15,7 (6,1)	12	78,4 (7,1)	58		x	x	x	x	x	x	x	x	x	x	x	x		85	32	22,4
	Placebo			14,7 (5,8)		77,3 (7,1)	57															142	47	14,8
De Deyn 1999	**Haloperidol**	1,2	AD, VD, mixed	7,9	12	medi an 82	53,9	BEHAVE AD								x		x				115	115	70,4
	Placebo			8,8		medi an 81	58,8															114	114	64,9
Devanand 1998	**Haloperidol**	0,5-3	AD	19,4 (11,6)	6	72,1 (9,6)	64,8	BPRS														44	40	90,9
	Placebo																					22	20	90,9
Petrie 1982	**Haloperidol**	4,6 (0,3)	prim/sec degen. Dement., VD	N / A	8	72,1 (5,3)	60	BPRS				x						x	x			20	20	60,0
	Placebo			N / A		72,5 (8,9)	55,5															22	22	59,1
Tariot 2006	**Haloperidol**	(1,9)	AD	12,73 (5,60)	10	83,55 (6,05)	67,0	BPRS					x	x	x	x	x	x	x	x		94	86	58,5
	Placebo			13,15 (5,44)		83,93 (6,66)	79,8															99	94	63,6
Auchus 1997	**Haloperidol**	3	AD	15,2 (4,6)	6	75,6 (7,5)	N / A	CMAI										x		x		6	6	N / A
	Placebo																					6	6	N / A
Allain 2000	**Haloperidol**	(3,53)	AD, VD, mixed	N / A	3	79,9 (7,9)	62					x	x			x		x	x	x		101	N / A	N / A
	Placebo			N / A		78,6 (7,3)	69															103	N / A	N / A
Teri 2000	**Haloperidol**	0,5-3	AD	13 (8)	16	75,3 (6,9)	59	CMAI													x	34	34	58,8
	Placebo			13 (8)		75,8 (6,2)	67															36	36	69,4
Barnes 1982	**Loxapine**	10,5	Dement.	N / A	8	N / A	N / A	BPRS				x						x		x		19	19	68,4
	Placebo			N / A		N / A	N / A															17	17	58,8
Petrie 1982	**Loxapine**	21,9 (1,6)	prim/sec degen. Dement., VD	N / A	8	73,5 (6,7)	36,8	BPRS				x						x	x			19	19	63,2
	Placebo			N / A		72,5 (8,9)	55,5															22	22	59,1
Pollock 2002	**Perphe-nazine**	6,5 (1,7)	AD, VD, mixed, LB	6,4 (6,4)	Up to 17 days	80,4 (9,0)	72,7	Neuro-behavioral Rating Scale										x				33	33	45
	Placebo			6,4 (6,8)		78,5 (8,5)	57,1															21	21	43
Kodijan 1986	**Pimozide**	Up to 12 mg	Senile Dement.	N / A	12	73,3	6	BPRS										x	x	x		18	18	N/A
	Placebo			N / A		81,1	9															23	23	N/A
Barnes 1982	**Thiori-dazine**	62,5	Dement.	N / A	8	N / A	N / A	BPRS				x						x		x		17	17	64,7
	Placebo			N / A		N / A	N / A															17	17	58,8
Finkel 1995	**Thiothixene**	0,25-18	Dement.	8,81	11	85	86	CMAI										x	x	x		16	16	N / A
	Placebo																					16	16	N / A
Allain 2000	**Tiapride**	(175,45)	AD, VD, mixed	N / A	3	80,3 (7,6)	62					x	x			x		x	x	x		102	N / A	N / A
	Placebo			N / A		78,6 (7,3)	69															103	N / A	N / A

N rand = number of patients randomized, N LOCF = number of patients with Last Observation Carried Forwards, C = Completers, Dement. = Dementia, AD = Alzheimer Dementia, VD = Vascular Dementia, LB = Lewy Body Dementia, MMSE = Mini Mental State Examination, NPI = Neuropsychiatric Inventory, BPRS = Brief Psychiatric Rating Scale, CMAI = Cohen Mansfield Agitation Inventory

EFFICACY ANALYSIS

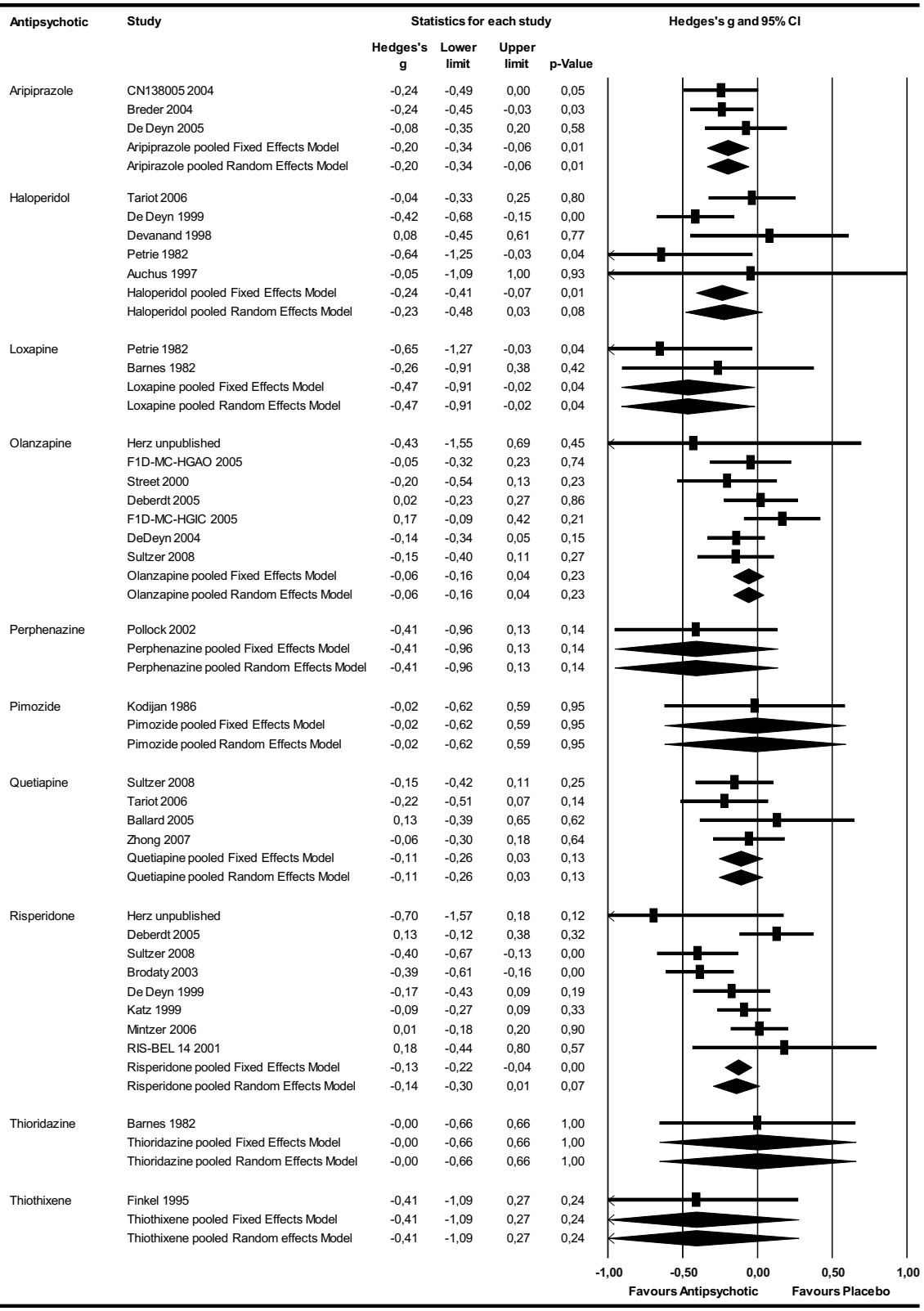
26 trials with 34 arms and 6.136 participants (antipsychotics: 4.065; placebo: 2.071) provided data on efficacy and were included in the efficacy analysis [21-46], three did not provide data [47-49]. It is worth mentioning that the papers published by Schneider et al. [49] and Sultzer et al. [43] both show results from the CATIE-AD trial, but deliver different data (see table 1). Pooled analysis of all antipsychotics revealed no heterogeneity (Q value: 31,5; df(Q): 26; p = 0,21; I^2: 17,6), therefore the fixed effects model is appropriate. Antipsychotics were generally more efficacious in treating BPSD than placebo, however effect-size was very low (Hedges's g = -0,13, CI: -0,19 – -0,08; p < 0,00001). Effect size of FGA (n = 352) versus placebo (n = 333) was slightly higher (Hedges's g = -0,24, CI: -0,39 – -0,09, p = 0,0002) than of SGA (n = 3.095) versus placebo (n = 1.813) (Hedges's g = -0,12, CI: -0,18 – -0,06, p = 0,0017) (see figure 2).

FIGURE 2: POOLED ANALYSES OF EFFICACY OF SECOND GENERATION ANTIPSYCHOTICS (SGA) AND FIRST GENERATION ANTIPSYCHOTICS (FGA)



In the pooled analysis of single drugs, test for heterogeneity was only significant for risperidone (Q value: 17,7; df(Q): 7,0; p = 0,01; I^2: 60,5), therefore homogeneity of studies was assumed for all other drugs. Loxapine showed the highest effect size (Hedges's g = -0,47, CI: -0,91 – -0,02, p = 0,04). Haloperidol also proved to be significantly efficacious (Hedges's g = -0,24, CI: -0,41 – -0,07, p = 0,01), whereas all other investigated FGA (perphenazine, pimozide, thioridazine, thiothixene) did not. Of the SGA, aripiprazole was the only efficacious antipsychotic (Hedges's g = -0,2, CI: -0,34 – -0,06, p = 0,01). Due to heterogeneity the random effects model had to be applied for risperidone, this failed, however, to reach significance (p = 0,07) (see figure 3). In the sensitivity analysis with results of long-term study results were comparable (FGA: Hedges's g = -0,22, CI: -0,37 – -0,08, p < 0,001; SGA: Hedges's g = -0,11, CI: -0,17 – -0,05, p < 0,001).

FIGURE 3: EFFICACY ANALYSIS OF ALL ANTIPSYCHOTIC AGENTS



Antipsychotic	Study	Hedges's g	Lower limit	Upper limit	p-Value
Aripiprazole	CN138005 2004	-0,24	-0,49	0,00	0,05
	Breder 2004	-0,24	-0,45	-0,03	0,03
	De Deyn 2005	-0,08	-0,35	0,20	0,58
	Aripiprazole pooled Fixed Effects Model	-0,20	-0,34	-0,06	0,01
	Aripirazole pooled Random Effects Model	-0,20	-0,34	-0,06	0,01
Haloperidol	Tariot 2006	-0,04	-0,33	0,25	0,80
	De Deyn 1999	-0,42	-0,68	-0,15	0,00
	Devanand 1998	0,08	-0,45	0,61	0,77
	Petrie 1982	-0,64	-1,25	-0,03	0,04
	Auchus 1997	-0,05	-1,09	1,00	0,93
	Haloperidol pooled Fixed Effects Model	-0,24	-0,41	-0,07	0,01
	Haloperidol pooled Random Effects Model	-0,23	-0,48	0,03	0,08
Loxapine	Petrie 1982	-0,65	-1,27	-0,03	0,04
	Barnes 1982	-0,26	-0,91	0,38	0,42
	Loxapine pooled Fixed Effects Model	-0,47	-0,91	-0,02	0,04
	Loxapine pooled Random Effects Model	-0,47	-0,91	-0,02	0,04
Olanzapine	Herz unpublished	-0,43	-1,55	0,69	0,45
	F1D-MC-HGAO 2005	-0,05	-0,32	0,23	0,74
	Street 2000	-0,20	-0,54	0,13	0,23
	Deberdt 2005	0,02	-0,23	0,27	0,86
	F1D-MC-HGIC 2005	0,17	-0,09	0,42	0,21
	DeDeyn 2004	-0,14	-0,34	0,05	0,15
	Sultzer 2008	-0,15	-0,40	0,11	0,27
	Olanzapine pooled Fixed Effects Model	-0,06	-0,16	0,04	0,23
	Olanzapine pooled Random Effects Model	-0,06	-0,16	0,04	0,23
Perphenazine	Pollock 2002	-0,41	-0,96	0,13	0,14
	Perphenazine pooled Fixed Effects Model	-0,41	-0,96	0,13	0,14
	Perphenazine pooled Random Effects Model	-0,41	-0,96	0,13	0,14
Pimozide	Kodijan 1986	-0,02	-0,62	0,59	0,95
	Pimozide pooled Fixed Effects Model	-0,02	-0,62	0,59	0,95
	Pimozide pooled Random Effects Model	-0,02	-0,62	0,59	0,95
Quetiapine	Sultzer 2008	-0,15	-0,42	0,11	0,25
	Tariot 2006	-0,22	-0,51	0,07	0,14
	Ballard 2005	0,13	-0,39	0,65	0,62
	Zhong 2007	-0,06	-0,30	0,18	0,64
	Quetiapine pooled Fixed Effects Model	-0,11	-0,26	0,03	0,13
	Quetiapine pooled Random Effects Model	-0,11	-0,26	0,03	0,13
Risperidone	Herz unpublished	-0,70	-1,57	0,18	0,12
	Deberdt 2005	0,13	-0,12	0,38	0,32
	Sultzer 2008	-0,40	-0,67	-0,13	0,00
	Brodaty 2003	-0,39	-0,61	-0,16	0,00
	De Deyn 1999	-0,17	-0,43	0,09	0,19
	Katz 1999	-0,09	-0,27	0,09	0,33
	Mintzer 2006	0,01	-0,18	0,20	0,90
	RIS-BEL 14 2001	0,18	-0,44	0,80	0,57
	Risperidone pooled Fixed Effects Model	-0,13	-0,22	-0,04	0,00
	Risperidone pooled Random Effects Model	-0,14	-0,30	0,01	0,07
Thioridazine	Barnes 1982	-0,00	-0,66	0,66	1,00
	Thioridazine pooled Fixed Effects Model	-0,00	-0,66	0,66	1,00
	Thioridazine pooled Random Effects Model	-0,00	-0,66	0,66	1,00
Thiothixene	Finkel 1995	-0,41	-1,09	0,27	0,24
	Thiothixene pooled Fixed Effects Model	-0,41	-1,09	0,27	0,24
	Thiothixene pooled Random effects Model	-0,41	-1,09	0,27	0,24

Test for heterogeneity:

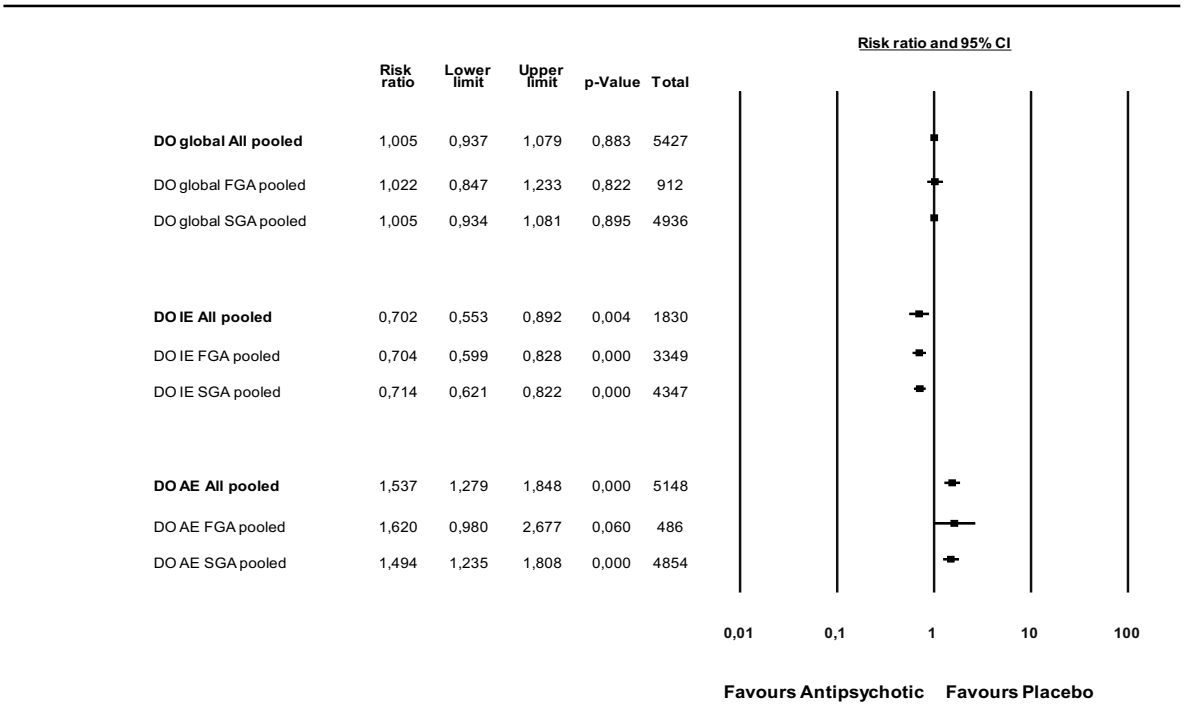
Aripiprazole: $Chi^2=1,02$, $df=2,00$, $(p=0,60)$, $I^2=0,00$ %
Haloperidol: $Chi^2=7,28$, $df=5,00$, $(p=0,20)$, $I^2=31,36$ %
Loxapine: $Chi^2=0,73$, $df=1,00$, $(p=0,39)$, $I^2=0,00$ %
Olanzapine: $Chi^2=8,40$, $df=6,00$, $(p=0,21)$, $I^2=28,58$ %
Perphenazine: $Chi^2=0,00$, $df=0,00$, $(p=1,00)$, $I^2=0,00$ %
Pimozide: $Chi^2=0,00$, $df=0,00$, $(p=1,00)$, $I^2=0,00$ %
Quetiapine: $Chi^2=1,25$, $df=3,00$, $(p=0,74)$, $I^2=0,00$ %
Risperidone: $Chi^2=17,71$, $df=7,00$, $(p=0,01)$, $I^2=60,48$ %
Thioridazine: $Chi^2=0,00$, $df=0,00$, $(p=1,00)$, $I^2=0,00$ %
Thiothixene: $Chi^2=0,00$, $df=0,00$, $(p=1,00)$, $I^2=0,00$ %

EFFECTIVENESS ANALYSIS

In the effectiveness analysis results for the pooled analysis of all antipsychotics vs. placebo and both subgroups FGA and SGA vs. placebo were rather alike. The tests for heterogeneity indicated the fixed effects model to be appropriate for all pooled analyses of groups and single drugs. The global drop-out rates between active comparator drugs and placebo were comparable. DOI, however, were more frequent in the placebo groups whereas DOAE were significantly more prevalent in the active comparator group (see figure 4).

The lowest global **drop-out** rates in relation to placebo were found for thiothixene, tiapride, and loxapine. Data on DAI were not available for perphenazine and thioridazine, on DOAE for perphenazine and thiothixene. For a detailed analysis of the individual drugs see table 3.

FIGURE 4: POOLED ANALYSES OF EFFECTIVENESS CRITERIA DROP-OUT



Total: number of patients in analysis, FGA: First Generation Antipsychotic, SGA: Second generation Antipsychotic, DO: Drop Out, IE: Inefficacy, AE: Adverse Events

TABLE 3: OVERVIEW AND RESULTS OF CLINICAL TRIALS INCLUDED IN THE EFFECTIVENESS ANALYSES

Antipsychotic	Study name	global Drop-Outs					Drop-Outs due to Adverse Events					Drop-Outs due to Inefficacy				
		RR	Lower	Upper	p-Value	Total	RR	Lower	Upper	p-Value	Total	RR	Lower	Upper	p-Value	Total
Aripiprazole	De Deyn 2005	0,96	0,53	1,74	0,90	208	1,37	0,54	3,47	0,50	208	0,48	0,12	1,87	0,29	208
	Breder 2004	0,87	0,69	1,09	0,23	487	1,28	0,77	2,13	0,34	487	0,74	0,51	1,07	0,10	487
	CN138005 2004						1,62	0,77	3,41	0,20	256					
	Fixed	*0,88*	*0,71*	*1,09*	*0,24*	*695*	*1,38*	*0,94*	*2,02*	*0,10*	*951*	*0,71*	*0,50*	*1,02*	*0,07*	*695*
	Random	*0,88*	*0,71*	*1,09*	*0,24*	*695*	*1,38*	*0,94*	*2,02*	*0,10*	*951*	*0,71*	*0,50*	*1,02*	*0,07*	*695*
Haloperidol	Tariot 2006	1,14	0,80	1,63	0,47	193	1,38	0,71	2,68	0,35	193	0,79	0,35	1,79	0,57	193
	De Deyn 1999	0,84	0,58	1,23	0,37	229										
	Allain 2000	1,34	0,74	2,41	0,33	204	2,89	1,19	7,03	0,02	204	0,13	0,02	1,00	0,05	204
	Auchus 1997	2,00	0,24	16,61	0,52	12	2,00	0,24	16,61	0,52	12					
	Petrie 1982	0,98	0,47	2,04	0,95	42						0,79	0,30	2,08	0,63	42
	Teri 2000	1,35	0,71	2,54	0,36	70										
	Fixed	*1,07*	*0,87*	*1,32*	*0,53*	*750*	*1,81*	*1,08*	*3,03*	*0,02*	*409*	*0,68*	*0,37*	*1,23*	*0,20*	*439*
	Random	*1,07*	*0,87*	*1,32*	*0,53*	*750*	*1,81*	*1,08*	*3,03*	*0,02*	*409*	*0,63*	*0,30*	*1,34*	*0,23*	*439*
Loxapine	Petrie 1982	0,90	0,42	1,95	0,79	41						0,50	0,15	1,66	0,25	41
	Barnes 1982	0,77	0,32	1,83	0,55	36	1,79	0,37	8,57	0,47	36					
	Fixed	*0,84*	*0,47*	*1,50*	*0,55*	*77*	*1,79*	*0,37*	*8,57*	*0,47*	*36*	*0,50*	*0,15*	*1,66*	*0,25*	*41*
	Random	*0,84*	*0,47*	*1,50*	*0,55*	*77*	*1,79*	*0,37*	*8,57*	*0,47*	*36*	*0,50*	*0,15*	*1,66*	*0,25*	*41*
Olanzapine	F1D-MC-HGAO 2005	1,00	0,77	1,30	1,00	238	1,11	0,44	2,77	0,83	238	0,94	0,66	1,33	0,71	238
	Street 2000	1,16	0,65	2,06	0,62	206	2,81	0,68	11,62	0,15	206	0,49	0,12	1,99	0,32	206
	Deberdt 2005	1,87	1,20	2,90	0,01	298	5,07	1,59	16,11	0,01	298					
	De Deyn 2004	0,95	0,71	1,29	0,75	649	3,42	1,41	8,31	0,01	649	0,50	0,32	0,77	0,00	649
	Herz unpublished	3,43	0,45	25,93	0,23	15	3,37	0,16	71,67	0,44	15	7,88	0,48	130,28	0,15	15
	Schneider 2006	0,94	0,83	1,06	0,30	242	4,87	2,18	10,86	0,00	242	0,57	0,44	0,75	0,00	242
	F1D-MC-HGIC 2005	1,50	1,02	2,20	0,04	268	2,78	0,99	7,83	0,05	268	1,26	0,58	2,76	0,56	268
	Fixed	*1,02*	*0,92*	*1,12*	*0,75*	*1916*	*3,02*	*2,03*	*4,50*	*0,00*	*1916*	*0,67*	*0,56*	*0,81*	*0,00*	*1618*
	Random	*1,14*	*0,93*	*1,40*	*0,20*	*1916*	*3,01*	*1,95*	*4,64*	*0,00*	*1916*	*0,73*	*0,50*	*1,04*	*0,08*	*1618*
Perphenazine	Pollock 2002	0,95	0,59	1,55	0,85	54										
	Fixed	*0,95*	*0,59*	*1,55*	*0,85*	*54*										
	Random	*0,95*	*0,59*	*1,55*	*0,85*	*54*										
Pimozide	Kodijan 1986	2,56	0,91	7,16	0,07	41	16,42	0,99	273,51	0,05	41	0,85	0,16	4,57	0,85	41
	Fixed	*2,56*	*0,91*	*7,16*	*0,07*	*41*	*16,42*	*0,99*	*273,51*	*0,05*	*41*	*0,85*	*0,16*	*4,57*	*0,85*	*41*
	Random	*2,56*	*0,91*	*7,16*	*0,07*	*41*	*16,42*	*0,99*	*273,51*	*0,05*	*41*	*0,85*	*0,16*	*4,57*	*0,85*	*41*
Quetiapine	Tariot 2006	0,88	0,59	1,30	0,52	190	0,84	0,39	1,81	0,65	190	0,73	0,31	1,69	0,46	190
	Schneider 2006	0,96	0,86	1,08	0,51	236	3,24	1,37	7,64	0,01	236	0,78	0,62	0,97	0,03	236
	Zhong 2007	1,03	0,74	1,42	0,88	333	1,15	0,56	2,34	0,71	333	0,73	0,37	1,45	0,37	333
	Ballard 2005	8,00	1,06	60,21	0,04	62										
	Paleacu 2007	1,60	0,63	4,05	0,32	40	1,00	0,07	14,90	1,00	40	1,20	0,44	3,30	0,72	40
	Fixed	*0,97*	*0,88*	*1,08*	*0,62*	*861*	*1,36*	*0,87*	*2,11*	*0,18*	*799*	*0,78*	*0,64*	*0,96*	*0,02*	*799*
	Random	*1,00*	*0,82*	*1,22*	*1,00*	*861*	*1,39*	*0,72*	*2,69*	*0,33*	*799*	*0,78*	*0,64*	*0,96*	*0,02*	*799*
Risperidone	De Deyn 1999	1,16	0,84	1,62	0,37	229										
	Herz unpublished	1,14	0,12	10,71	0,91	22						3,00	0,16	55,72	0,46	22
	Schneider 2006	0,91	0,80	1,04	0,17	227	3,58	1,52	8,43	0,00	227	0,64	0,49	0,83	0,00	227
	Brodaty 2003	0,82	0,59	1,14	0,23	337	1,60	0,85	3,02	0,15	337	0,49	0,28	0,86	0,01	337
	Katz 1999	1,17	0,88	1,56	0,28	625	1,34	0,85	2,12	0,21	625	0,86	0,41	1,83	0,70	625
	Mintzer 2006	1,01	0,74	1,38	0,94	473	1,05	0,62	1,79	0,84	473	0,89	0,44	1,77	0,73	473
	RIS-BEL 14 2001	0,95	0,28	3,27	0,94	39						0,48	0,10	2,30	0,35	39
	Deberdt 2005						2,72	0,82	9,05	0,10	290					
	Fixed	*0,96*	*0,87*	*1,07*	*0,47*	*1952*	*1,50*	*1,13*	*1,98*	*0,00*	*1952*	*0,65*	*0,52*	*0,81*	*0,00*	*1723*
	Random	*0,96*	*0,87*	*1,07*	*0,47*	*1952*	*1,61*	*1,09*	*2,37*	*0,02*	*1952*	*0,65*	*0,52*	*0,81*	*0,00*	*1723*
Thioridazine	Barnes 1982	0,86	0,36	2,02	0,72	34	2,00	0,42	9,50	0,38	34					
	Fixed	*0,86*	*0,36*	*2,02*	*0,72*	*34*	*2,00*	*0,42*	*9,50*	*0,38*	*34*					
	Random	*0,86*	*0,36*	*2,02*	*0,72*	*34*	*2,00*	*0,42*	*9,50*	*0,38*	*34*					
Thiothixene	Finkel 1995	0,14	0,01	2,56	0,19	32						0,33	0,01	7,62	0,49	32
	Fixed	*0,14*	*0,01*	*2,56*	*0,19*	*32*						*0,33*	*0,01*	*7,62*	*0,49*	*32*
	Random	*0,14*	*0,01*	*2,56*	*0,19*	*32*						*0,33*	*0,01*	*7,62*	*0,49*	*32*
Tiapride	Allain 2000	0,63	0,30	1,32	0,22	205	0,84	0,27	2,67	0,77	205	0,13	0,02	0,99	0,05	205
	Fixed	*0,63*	*0,30*	*1,32*	*0,22*	*205*	*0,84*	*0,27*	*2,67*	*0,77*	*205*	*0,13*	*0,02*	*0,99*	*0,05*	*205*
	Random	*0,63*	*0,30*	*1,32*	*0,22*	*205*	*0,84*	*0,27*	*2,67*	*0,77*	*205*	*0,13*	*0,02*	*0,99*	*0,05*	*205*

Fixed = Fixed effects model, Random = Random Effects Model, RR = Risk ratio, Lower = Lower limit, Upper = Upper limit, Total = Total sample size

TOLERABILITY ANALYSIS

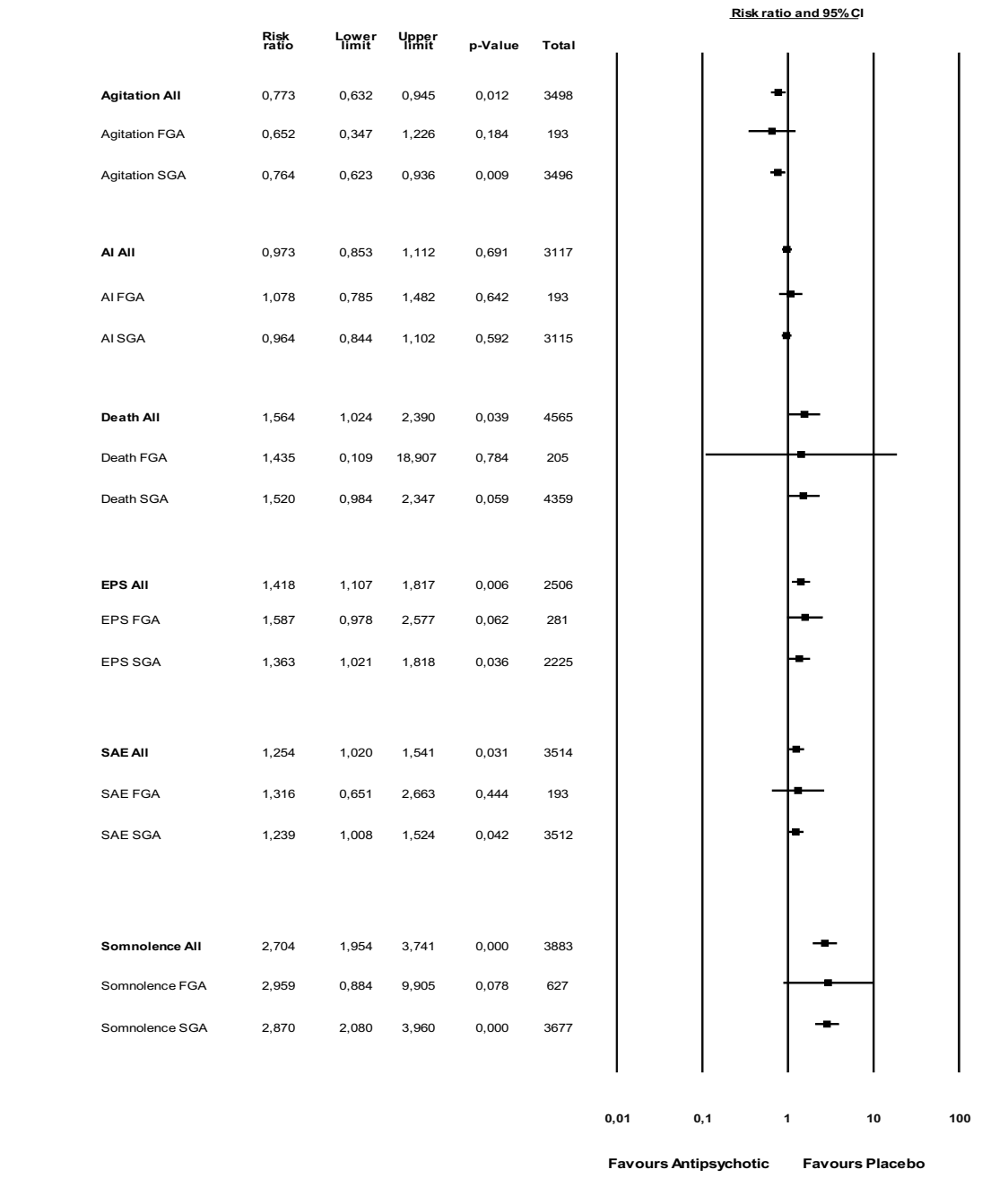
The tests for heterogeneity indicated the fixed effects model to be appropriate for all pooled analyses of groups and single drugs with the exception of somnolence. The use of antipsychotics goes along with significantly higher rates of **somnolence** (RR = 2,7; p < 0,0001), **death** (RR = 1,6; p = 0,039), **EPS** (RR = 1,4; p = 0,006), and **SAE** (RR: 1.3; p=0.031). Agitation was lower when using antipsychotics (RR: 0,8; p = 0,012). For **accidental injuries** no difference was found between antipsychotics and placebo (RR = 0,97; p = 0,69) (see figure 5).

There was no difference in tolerability profile between SGA and FGA. For the detailed analysis of FGA and SGA compared to placebo see table 3.

Concerning single antipsychotic drugs the risk ratio for **agitation** was significant only for aripiprazole (RR = 0,57; p = 0,03). For haloperidol (RR: = 0,65; p = 0,18), and quetiapine (RR = 0,66; p = 0,49) the risk ratio was still moderate, yet not significant (no data for loxapine, thioridazine, thiothixene, perphenazine). **Accidental injury** (no data for loxapine, thioridazine, tiapride, thiothixene, pimozide, perphenazine), **death** (no data for loxapine, thioridazine, thiothixene, pimozide, perphenazine), and **SAE** (no data for loxapine, thioridazine, tiapride, thiothixene, pimozide, perphenazine) were not significantly different for any of the investigated single drugs. **EPS** was significantly worse for olanzapine (RR = 17,04; p = 0,006), haloperidol (RR = 2,02; p = 0,002), loxapine (RR = 2,75; p = 0,041), and risperidone (RR = 1,72; p = 0,002) (no data for thiothixene, pimozide, perphenazine).

Concerning **somnolence** the random effects model had to be used (test for heterogeneity: Q value: 35,8; df(Q): 17,0; p = 0,005; I^2: 52,5). Quetiapine (RR = 4,9; p < 0,0001), olanzapine (RR = 3,7; p < 0,0001) and risperidone (RR = 2,0; p = 0,000) induced significantly more somnolence than placebo. Data of FGA were only available for haloperidol (RR = 3,0; p = 0,07) and tiapride (RR = 1,01; p = 0,98) (no data for loxapine, thioridazine, thiothixene, pimozide, perphenazine).

FIGURE 5: POOLED ANALYSES OF TOLERABILITY CRITERIA AGITATION, ACCIDENTAL INJURY (AI), DEATH, EXTRAPYRAMIDAL SYMPTOMS (EPS), SERIOUS ADVERSE ADVENTS (SAE) AND SOMNOLENCE



Total: number of patients in analysis, FGA: First Generation Antipsychotic, SGA: Second Generation Antipsychotic

TABLE 4: OVERVIEW AND RESULTS OF CLINICAL TRIALS INCLUDED IN THE TOLERABILITY ANALYSES

		Death					SERIOUS ADVERSE EVENTS					SOMNOLENCE					AGITATION					Accidental Injuries					EPS				
Antipsychotic	Study name	RR	Lower	Upper	p-Value	Total	RR	Lower	Upper	p-Value	Total	RR	Lower	Upper	p-Value	Total	RR	Lower	Upper	p-Value	Total	RR	Lower	Upper	p-Value	Total	RR	Lower	Upper	p-Value	Total
Aripiprazole	CN138005 2004	1,05	0,22	5,10	0,95	256	0,99	0,52	1,87	0,97	256																			
	De Deyn 2005	2,89	0,12	70,08	0,51	208	1,71	0,79	3,69	0,17	208																1,20	0,33	4,35	0,78	208
	Breder 2004	1,24	0,42	3,66	0,70	487						2,07	0,73	5,82	0,17	487	0,57	0,34	0,93	0,03	487	1,28	0,85	1,93	0,24	487	1,28	0,57	2,85	0,55	487
	Fixed	1,25	0,53	2,97	0,61	951	1,23	0,76	2,02	0,40	464	2,07	0,73	5,82	0,17	487	0,57	0,34	0,93	0,03	487	1,28	0,85	1,93	0,24	487	1,25	0,63	2,48	0,52	695
	Random	1,25	0,53	2,97	0,61	951	1,24	0,73	2,12	0,42	464	2,07	0,73	5,82	0,17	487	0,57	0,34	0,93	0,03	487	1,28	0,85	1,93	0,24	487	1,25	0,63	2,48	0,52	695
Haloperidol	Tariot 2006	1,84	0,56	6,09	0,32	193	1,32	0,65	2,66	0,44	193	8,95	3,30	24,26	0,00	193	0,65	0,35	1,23	0,18	193	1,08	0,78	1,48	0,64	193					
	Allain 2000	2,04	0,19	22,14	0,56	204						1,15	0,46	2,86	0,77	204											1,93	1,17	3,18	0,01	204
	De Deyn 1999											2,78	1,03	7,45	0,04	229															
	Petrie 1982																										2,48	0,90	6,80	0,08	42
	Fixed	1,88	0,65	5,48	0,25	397	1,32	0,65	2,66	0,44	193	2,88	1,65	5,02	0,00	626	0,65	0,35	1,23	0,18	193	1,08	0,78	1,48	0,64	193	2,02	1,29	3,17	0,00	246
	Random	1,88	0,65	5,48	0,25	397	1,32	0,65	2,66	0,44	193	3,02	0,93	9,76	0,07	626	0,65	0,35	1,23	0,18	193	1,08	0,78	1,48	0,64	193	2,02	1,29	3,17	0,00	246
Loxapine	Petrie 1982																										2,32	0,83	6,50	0,11	41
	Barnes 1982																										9,90	0,59	166,78	0,11	36
	Fixed																										2,75	1,04	7,24	0,04	77
	Random																										2,75	1,04	7,24	0,04	77
Olanzapine	Deberdt 2005	3,24	0,17	62,18	0,43	298						2,71	1,33	5,50	0,01	298	1,31	0,73	2,35	0,36	298	1,24	0,63	2,46	0,53	298					
	De Deyn 2004	1,86	0,43	8,03	0,41	649	4,34	1,06	17,81	0,04	649						0,55	0,26	1,18	0,13	649										
	Street 2000	3,30	0,19	58,61	0,42	206	3,84	0,95	15,60	0,06	206	4,53	1,48	13,91	0,01	206	1,33	0,47	3,74	0,59	206	1,26	0,71	2,23	0,42	206					
	Schneider 2006	0,47	0,05	4,48	0,51	242	1,05	0,55	1,99	0,89	242	4,87	2,18	10,86	0,00	242	0,71	0,30	1,70	0,44	242	1,15	0,64	2,07	0,64	242	17,04	2,25	128,95	0,01	242
	F1D-MC-HGIC 2005											3,79	1,38	10,43	0,01	268						1,77	0,74	4,23	0,20	268					
	Fixed	1,60	0,56	4,58	0,38	1395	1,56	0,91	2,67	0,11	1097	3,69	2,39	5,70	0,00	1014	0,94	0,64	1,38	0,76	1395	1,28	0,93	1,77	0,13	1014	17,04	2,25	128,95	0,01	242
	Random	1,60	0,56	4,58	0,38	1395	2,20	0,78	6,22	0,14	1097	3,69	2,39	5,70	0,00	1014	0,92	0,59	1,45	0,73	1395	1,28	0,93	1,77	0,13	1014	17,04	2,25	128,95	0,01	242
Quetiapine	Schneider 2006	1,51	0,31	7,33	0,61	236	1,35	0,74	2,46	0,33	236	4,53	2,01	10,24	0,00	236	1,19	0,56	2,50	0,65	236	0,50	0,22	1,14	0,10	236	3,02	0,28	32,85	0,36	236
	Ballard 2005	3,00	0,13	70,92	0,50	62																									
	Zhong 2007	1,91	0,57	6,44	0,30	333	0,93	0,45	1,95	0,85	333	4,01	0,96	16,76	0,06	333											0,53	0,25	1,16	0,11	333
	Tariot 2006	0,54	0,10	2,90	0,48	190	0,91	0,41	2,00	0,81	190	6,26	2,25	17,40	0,00	190	0,36	0,16	0,81	0,01	190	0,96	0,68	1,34	0,81	190					
	Fixed	1,38	0,62	3,10	0,43	821	1,09	0,73	1,63	0,66	759	4,93	2,75	8,82	0,00	759	0,69	0,40	1,19	0,18	426	0,87	0,64	1,19	0,39	426	0,63	0,30	1,32	0,22	569
	Random	1,38	0,62	3,10	0,43	821	1,09	0,73	1,63	0,66	759	4,93	2,75	8,82	0,00	759	0,66	0,21	2,12	0,49	426	0,78	0,43	1,40	0,40	426	0,87	0,19	3,97	0,85	569
Risperidone	Schneider 2006	0,56	0,06	5,27	0,61	227	0,79	0,38	1,67	0,54	227	3,10	1,29	7,47	0,01	227	0,60	0,22	1,60	0,30	227	0,80	0,39	1,61	0,52	227	16,71	2,18	128,22	0,01	227
	Brodaty 2003	1,53	0,44	5,31	0,51	337	1,90	1,05	3,43	0,03	337	1,44	1,04	2,00	0,03	337	0,80	0,53	1,20	0,28	337	0,97	0,73	1,29	0,83	337	1,47	0,95	2,29	0,09	337
	Katz 1999	1,76	0,69	4,53	0,24	625	1,16	0,74	1,83	0,52	625	2,33	1,34	4,07	0,00	625	0,68	0,39	1,20	0,18	625	0,83	0,65	1,05	0,12	625	1,88	1,04	3,39	0,04	625
	Mintzer 2006	5,06	0,24	104,91	0,29	473	1,08	0,68	1,70	0,75	473	3,50	1,83	6,68	0,00	473	1,20	0,63	2,28	0,57	473	0,89	0,52	1,54	0,68	473					
	Deberdt 2005											2,22	1,08	4,57	0,03	290	1,11	0,61	2,02	0,74	290	0,77	0,36	1,63	0,49	290					
	De Deyn 1999											3,77	1,46	9,74	0,01	229															
	Fixed	1,60	0,80	3,20	0,19	1662	1,19	0,91	1,55	0,19	1662	2,03	1,61	2,54	0,00	2181	0,86	0,67	1,10	0,23	1952	0,87	0,74	1,03	0,11	1952	1,72	1,21	2,44	0,00	1189
	Random	1,60	0,80	3,20	0,19	1662	1,19	0,88	1,61	0,25	1662	2,35	1,64	3,35	0,00	2181	0,86	0,67	1,10	0,23	1952	0,87	0,74	1,03	0,11	1952	2,07	1,03	4,19	0,04	1189
Thioridazine	Barnes 1982																										7,00	0,39	125,99	0,19	34
																											7,00	0,39	125,99	0,19	34
																											7,00	0,39	125,99	0,19	34
Tiapride	Allain 2000	1,01	0,06	15,93	0,99	205						1,01	0,39	2,59	0,98	205											0,90	0,49	1,66	0,73	205
	Fixed	1,01	0,06	15,93	0,99	205						1,01	0,39	2,59	0,98	205											0,90	0,49	1,66	0,73	205
	Random	1,01	0,06	15,93	0,99	205						1,01	0,39	2,59	0,98	205											0,90	0,49	1,66	0,73	205

Fixed = Fixed effects model, Random = Random Effects Model, RR = Risk ratio, Lower = Lower limit, Upper = Upper limit, Total = Total sample size

Data on **akathisia** were rare. Dichotomous data were only provided by six studies [23, 24, 33, 42, 48, 49] and continuous data via Barnes Global Scale only by two [31, 36]. There were no data for FGA. For the occurrence of akathisia measured as event, there is no significant difference found between SGA and Placebo (see figure 6). The analysis of Barnes Global Scale shows a tendency for SGA to be superior compared to placebo, but with no significance (see figure 7). The risperidone treatment arm from the trial by Herz goes along with an advantage for the antipsychotic (Hedges's g = -1,128; CI: -2,040 – -0,217; p = 0,015).

For the analysis of **dyskinesia** data was only provided for SGA. Four trials were included in the analysis of dichotomous data on dyskinesia [24, 32, 33, 49] and five in the analysis of continuous data using the Abnormal Involuntary Movement Scale (AIMS) [31, 39, 44, 46, 48]. For both analyses no significant results were found between antipsychotics and placebo (see figure 8 and 9).

For the analysis of the occurrence of **parkinsonism** seven studies provided dichotomous data [23, 24, 32, 33, 42, 48, 49] and eight continuous data (Simpson-Angus Scale, SAS) [21, 31, 36, 37, 39, 44, 46, 48]. Pooled results from dichotomous and continuous data revealed a higher occurrence of parkinsonism or parkinsonoid in the antipsychotic group (see figure 10 and 11). In the dichotomous data set the random effects model has to be chosen which was of borderline significance only (RR = 1,679; p = 0,053).

Within the single drug analysis significant effects were only found for haloperidol and risperidone. For risperidone this effect was confirmed in the dichotomous data set only (RR = 1,754; p = 0,014; fixed model to be applied). In the continuous data set the random effects model had to be chosen, which was not significant.

FIGURE 6: AKATHISIA ANALYSIS

Antipsychotic	Study name	Risk ratio	Lower limit	Upper limit	p-Value
Olanzapine	Deberdt 2005	0,922	0,236	3,606	0,907
	F1D-MC-HGAO 2005	1,377	0,450	4,216	0,576
	Street 2000	0,591	0,154	2,274	0,444
	Schneider 2006	4,248	0,175	103,212	0,374
	F1D-MC-HGIC 2005	0,169	0,007	4,119	0,276
	Olanzapine pooled Fixed Effects Model	0,948	0,474	1,896	0,881
	Olanzapine pooled Random Effects Model	0,948	0,474	1,896	0,881
Quetiapine	Schneider 2006	4,516	0,186	109,690	0,354
	Paleacu 2007	0,333	0,014	7,724	0,493
	Quetiapine pooled Fixed Effects Model	1,203	0,128	11,290	0,871
	Quetiapine pooled Fixed Effects Model	1,209	0,094	15,540	0,884
Risperidone	Deberdt 2005	0,799	0,195	3,274	0,756
	Risperidone pooled Fixed Effects Model	0,799	0,195	3,274	0,756
	Risperidone pooled Random Effects Model	0,799	0,195	3,274	0,756
Overall	All pooled Fixed Effects Model	0,935	0,514	1,703	0,827
	All pooled Random Effects Model	0,932	0,509	1,705	0,818

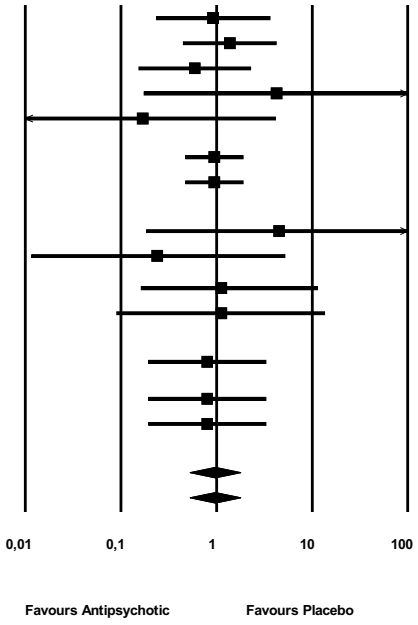


FIGURE 7: BARNES GLOBAL AKATHISIA SCALE

Antipsychotic	Study	Hedges's g	Lower limit	Upper limit	p-Value
Aripiprazole	De Deyn 2005	-0,103	-0,379	0,173	0,464
Olanzapine	Herz unpublished	-0,320	-1,435	0,795	0,574
Risperidone	Herz unpublished	-1,128	-2,040	-0,217	0,015
Overall	All pooled Fixed Effects Model	-0,196	-0,453	0,061	0,135
	All pooled Random Effects Model	-0,196	-0,453	0,061	0,135

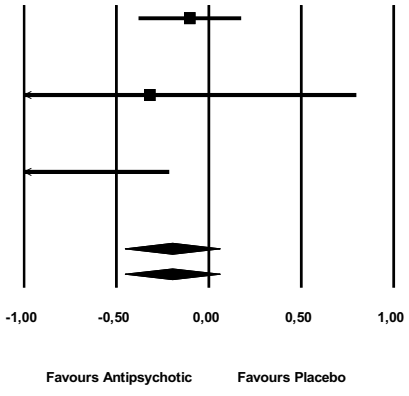


FIGURE 8: DYSKINESIA ANALYSIS

Antipsychotic	Study name	Risk ratio	Lower limit	Upper limit	p-Value
Olanzapine	Deberdt 2005	0,922	0,285	2,984	0,892
	De Deyn 2004	0,347	0,112	1,077	0,067
	Schneider 2006	1,420	0,090	22,435	0,803
	F1D-MC-HGIC 2005	3,559	0,186	68,157	0,399
	Olanzapine pooled Fixed Effects Model	0,673	0,316	1,433	0,304
	Olanzapine pooled Random Effects Model	0,679	0,313	1,477	0,329
Quetiapine	Schneider 2006	3,021	0,278	32,850	0,364
	Quetiapine pooled Fixed Effects Model	3,021	0,278	32,850	0,364
	Quetiapine pooled Random Effects Model	3,021	0,278	32,850	0,364
Risperidone	Deberdt 2005	0,839	0,252	2,797	0,775
	Schneider 2006	3,341	0,308	36,295	0,322
	Risperidone pooled Fixed Effects Model	1,111	0,379	3,253	0,848
	Risperidone pooled Random Effects Model	1,123	0,372	3,388	0,837
Overall	All pooled Fixed Effects Model	0,864	0,475	1,572	0,632
	All pooled Random Effects Model	0,876	0,474	1,618	0,672

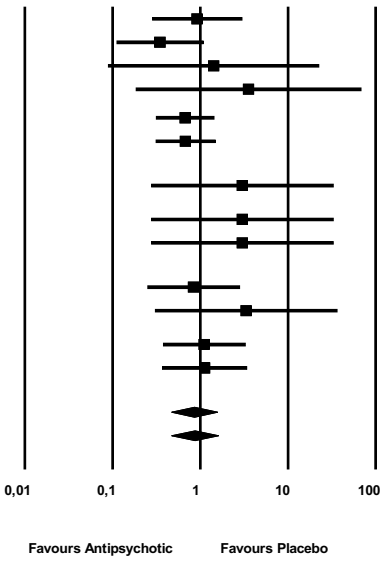
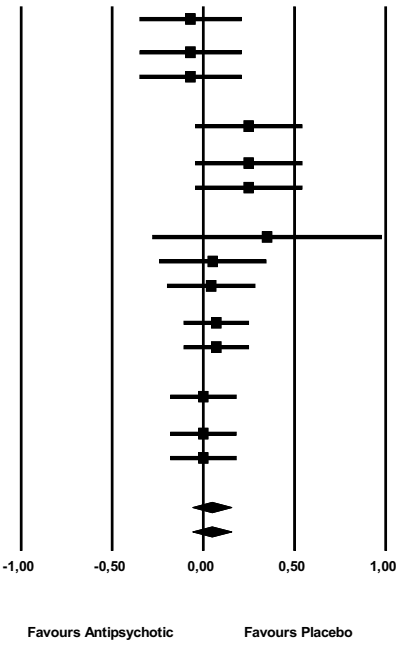


FIGURE 9: ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Antipsychotic	Study	Hedges's g	Lower limit	Upper limit	p-Value
Aripiprazole	De Deyn 2005	-0,071	-0,348	0,207	0,618
	Aripiprazole pooled Fixed Effects Model	-0,071	-0,348	0,207	0,618
	Aripiprazole pooled Random Effects Model	-0,071	-0,348	0,207	0,618
Haloperidol	Tariot 2006	0,249	-0,043	0,542	0,095
	Haloperidol pooled Fixed Effects Model	0,249	-0,043	0,542	0,095
	Haloperidol pooled Random Effects Model	0,249	-0,043	0,542	0,095
Quetiapine	Paleacu 2007	0,349	-0,278	0,977	0,275
	Tariot 2006	0,051	-0,241	0,344	0,730
	Zhong 2007	0,043	-0,197	0,283	0,725
	Quetiapine pooled Fixed Effects Model	0,071	-0,107	0,248	0,435
	Quetiapine pooled Random Effects Model	0,071	-0,107	0,248	0,435
Risperidone	Mintzer 2006	0,000	-0,180	0,180	1,000
	Risperidone pooled Fixed Effects Model	0,000	-0,180	0,180	1,000
	Risperidone pooled Random Effects Model	0,000	-0,180	0,180	1,000
Overall	All pooled Fixed Effects Model	0,049	-0,059	0,156	0,374
	All pooled Random Effects Model	0,049	-0,059	0,156	0,374

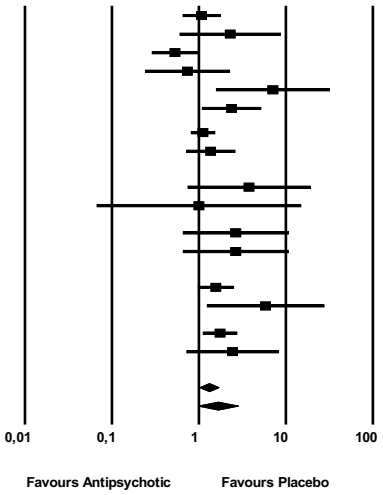


Test for heterogeneity:

Aripiprazole: Chi^2=0,00, df=0,00, (p=1,00), I^2=0,00 %
Quetiapine: Chi^2=0,83, df=2,00, (p=0,66), I^2=0,00 %
Olanzapine: Chi^2=8,40, df=6,00, (p=0,21), I^2=28,58 %
Haloperidol: Chi^2=0,00, df=0,00, (p=1,00), I^2=0,00 %
Risperidone: Chi^2=0,00, df=0,00, (p=1,00), I^2=0,00 %
Overall: Chi^2=3,68, df=5,00, (p=0,60), I^2=0,00 %

FIGURE 10: PARKINSONISM ANALYSIS

Antipsychotic	Study name	Risk ratio	Lower limit	Upper limit	p-Value
Olanzapine	Deberdt 2005	1,075	0,655	1,764	0,774
	F1D-MC-HGAO 2005	2,294	0,608	8,662	0,220
	De Deyn 2004	0,532	0,290	0,973	0,040
	Street 2000	0,739	0,243	2,249	0,594
	Schneider 2006	7,100	1,590	31,708	0,010
	F1D-MC-HGIC 2005	2,384	1,098	5,175	0,028
	Olanzapine pooled Fixed Effects Model	1,114	0,816	1,521	0,497
	Olanzapine pooled Random Effects Model	1,371	0,722	2,604	0,335
Quetiapine	Schneider 2006	3,777	0,748	19,064	0,108
	Paleacu 2007	1,000	0,067	14,904	1,000
	Quetiapine pooled Fixed Effects Model	2,658	0,663	10,659	0,168
	Quetiapine pooled Random Effects Model	2,658	0,663	10,659	0,168
Risperidone	Deberdt 2005	1,572	0,985	2,508	0,058
	Schneider 2006	5,847	1,243	27,502	0,025
	Risperidone pooled Fixed Effects Model	1,754	1,122	2,743	0,014
	Risperidone pooled Random Effects Model	2,443	0,724	8,240	0,150
Overall	All pooled Fixed Effects Model	1,323	1,029	1,701	0,029
	All pooled Random Effects Model	1,679	0,993	2,838	0,053

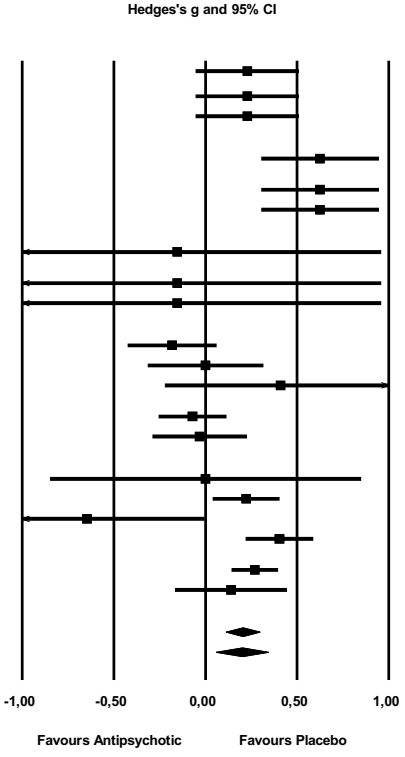


Test for heterogeneity:

Olanzapine: Chi^2=17,02, df=5,00, (p=0,005), I^2=70,62 %
Risperidone : Chi^2=2,53, df=1,00, (p=0,11), I^2=60,54 %
Quetiapine: Chi^2=0,68, df=1,00, (p=0,41), I^2=0,00 %
Overall: Chi^2=23,90 df=9,00, (p=0,005), I^2=62,35 %

FIGURE 11: SIMPSON-ANGUS SCALE (SAS)

Antipsychotic	Study	Hedges's g	Lower limit	Upper limit	p-Value
Aripiprazole	De Deyn 2005	0,228	-0,051	0,507	0,109
	Aripirazole pooled Fixed Effects Model	0,228	-0,051	0,507	0,109
	Aripirazole pooled Random Effects Model	0,228	-0,051	0,507	0,109
Haloperidol	Tariot 2006	0,625	0,307	0,944	0,000
	Haloperidol pooled Fixed Effects Model	0,625	0,307	0,944	0,000
	Haloperidol pooled Random Effects Model	0,625	0,307	0,944	0,000
Olanzapine	Herz unpublished	-0,154	-1,263	0,956	0,786
	Olanzapine pooled Fixed Effects Model	-0,154	-1,263	0,956	0,786
	Olanzapine pooled Random Effects Model	-0,154	-1,263	0,956	0,786
Quetiapine	Zhong 2007	-0,182	-0,422	0,058	0,138
	Tariot 2006	0,000	-0,313	0,313	1,000
	Paleacu 2007	0,410	-0,220	1,039	0,202
	Quetiapine pooled Fixed Effects Model	-0,071	-0,253	0,112	0,448
	Quetiapine pooled Random Effects Model	-0,032	-0,288	0,224	0,807
Risperidone	Herz unpublished	0,000	-0,845	0,845	1,000
	Katz 1999	0,222	0,042	0,402	0,016
	RIS-BEL 14 2001	-0,647	-1,286	-0,008	0,047
	Mintzer 2006	0,404	0,222	0,586	0,000
	Risperidone pooled Fixed Effects Model	0,269	0,145	0,393	0,000
	Risperidone pooled Random Effects Model	0,139	-0,164	0,443	0,367
Overall	All pooled Fixed Effects Model	0,205	0,113	0,297	0,000
	All pooled Random Effects Model	0,201	0,059	0,343	0,005



Test for heterogeneity:

Aripiprazole: Chi^2=0,00, df=0,00, (p=1,00), I^2=0,00 %
Olanzapine: Chi^2=0,00, df=0,00, (p=1,00), I^2=0,00 %
Risperidone : Chi^2=10,65, df=3,00, (p=0,01), I^2=71,82 %
Haloperidol: Chi^2=0,00, df=0,00, (p=1,00), I^2=0,00 %
Quetiapine: Chi^2=3,26, df=2,00, (p=0,20), I^2=38,62 %
Overall: Chi^2=30,83, df=9,00, (p=0,00), I^2=70,81 %

COGNITION ANALYSIS

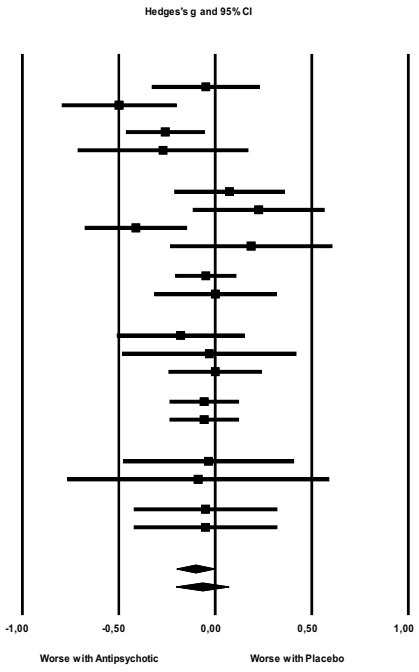
The pooled analyses of all antipsychotics compared to placebo revealed a trend towards a deterioration in cognitive functioning, however, with very small effect size (Hedge's g random effects model: -0,06; p = 0,30, fixed effects model: -0,10; p = 0,04). The random effects model had to be chosen due to heterogeneity of variance (Q value: 20,4; df(Q): 12,0; p = 0,06; I^2: 41,2).

For the SGA the respective data could be taken from figure 12. The results are quite alike. Even if choosing the fixed effects model, a Hedges's g of 0,1 is minimal. The mean difference in MMSE score between SGA and placebo would only be 0,3 points (calculated as a weighted difference in means using Comprehensive Meta-analysis version two [20]). The results of the sensitivity analysis were similar. The funnel plot did not suggest a publication bias.

Both trials with aripiprazole showed a worsening with the antipsychotic, being significant in one trial [31], and not significant in the other [22]. The pooled analysis is only significant for the fixed effects model (p = 0,012), but not for the random effects model (p = 0,229). Three studies on olanzapine reported no or minimal differences between placebo [23, 42, 43]. A fourth study, that included patients with a particularly high MMSE Score of 21,5 points found a significant deterioration with olanzapine as compared to placebo [24]. The pooled analysis did not reveal significant results, neither in the fixed effects model (p = 0,540), nor in the random effects model (p = 0.995). The three studies with quetiapine consistently showed no difference compared to placebo [43, 44, 46]. Results of the fixed and random effects models are identical (p = 0,529). The two studies with risperidone exhibited no difference as compared to placebo [21, 43]. The pooled analysis results for risperidone are identical in the fixed and random effects models (p = 0,790). For haloperidol we found one short-term trial with no differences to placebo (Hedges's g = -0,037; 95% CI: -0,373 – 0,300; p = 0,831) [44]. For one long-term trial the results were very much the same (Hedges's g = -0,107; 95% CI: -0,571 – 0,357; p = 0,651) [45]. The pooled results for haloperidol are identical for the fixed and the random effects model (Hedges's g = -0,061; 95% CI: -0,333 – 0,211; p = 0,661).

Figure 12: Changes in the Mini Mental State Exam during treatment with antipsychotics. Pooled analysis of second generation antipsychotics compared to placebo

Antipsychotic	Study	Hedges's g	Lower limit	Upper limit	p-Value
Aripiprazole	CN138005 2004	-0,049	-0,326	0,229	0,730
	De Deyn 2005	-0,498	-0,794	-0,202	0,001
	Aripirazole pooled Fixed Effects Model	-0,259	-0,461	-0,057	0,012
	Aripirazole pooled Random Effects Model	-0,270	-0,710	0,170	0,229
Olanzapine	F1D-MC-HGAO 2005	0,074	-0,211	0,359	0,612
	Street 2000	0,225	-0,114	0,564	0,194
	F1D-MC-HGIC 2005	-0,411	-0,675	-0,148	0,002
	Sultzer 2008	0,186	-0,233	0,605	0,384
	Olanzapine pooled Fixed Effects Model	-0,049	-0,205	0,107	0,540
	Olanzapine pooled Random Effects Model	0,001	-0,315	0,317	0,995
Quetiapine	Tariot 2006	-0,179	-0,508	0,150	0,287
	Sultzer 2008	-0,031	-0,480	0,418	0,892
	Zhong 2007	0,000	-0,240	0,240	1,000
	Quetiapine pooled Fixed Effects Model	-0,057	-0,235	0,121	0,529
	Quetiapine pooled Random Effects Model	-0,057	-0,235	0,121	0,529
Risperidone	Sultzer 2008	-0,034	-0,475	0,407	0,880
	RIS-BEL 14 2001	-0,089	-0,766	0,589	0,798
	Risperidone pooled Fixed Effects Model	-0,050	-0,420	0,319	0,790
	Risperidone pooled Random Effects Model	-0,050	-0,420	0,319	0,790
Overall	All pooled Fixed Effects Model	-0,101	-0,198	-0,003	0,044
	All pooled Random Effects Model	-0,066	-0,202	0,070	0,343



Test for heterogeneity:

Aripiprazole: Chi^2=4.71, df=1.00, (p=0.03), I^2=78.77 %
Quetiapine: Chi^2=0.76, df=2.00, (p=0.69), I^2=0.00 %
Overall: Chi^2=20.26, df=10,00, (p=0.03), I^2=50.56 %
Olanzapine: Chi^2=11.70, df=3.00, (p=0.01), I^2=74.35 %
Risperidone: Chi^2=0.02, df=1.00, (p=0.89), I^2=0.00 %

DISCUSSION

DEMENTIA, BPSD AND ITS TREATMENTS

The word “Dementia” is derived from the Latin “de” (out of) and “mens” (mind) and means “out of one’s mind”. In the early 19th century the French Psychiatrist Jean Etienne Dominique Esquirol gave a short but accurate definition of dementia as “a cerebral affection … characterized by a weakening of the sensibility, understanding, and will” [50]. It is remarkable that Esquirol not only focuses on cognitive impairment, but also on other manifestations, such as apathy, deterioration in social behaviour, occasional aggressiveness, delusional ideas and hallucinations [51]. His definition does not deviate a great deal from the ones more than 150 years later. The British dementia guideline defines dementia “as a clinical syndrome … characterized by global cognitive impairment, which represents a decline from previous level of functioning, and is associated with impairment in functional abilities and, in many cases, behavioural and psychiatric disturbances” [52].

Several of these formal definitions exist, such as the mentionable International Classification of Diseases (ICD) 10: “a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capability, language, and judgment. Consciousness is not impaired. Impairments of cognitive function are commonly accompanied, occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. The syndrome occurs in Alzheimer’s disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain” [53].

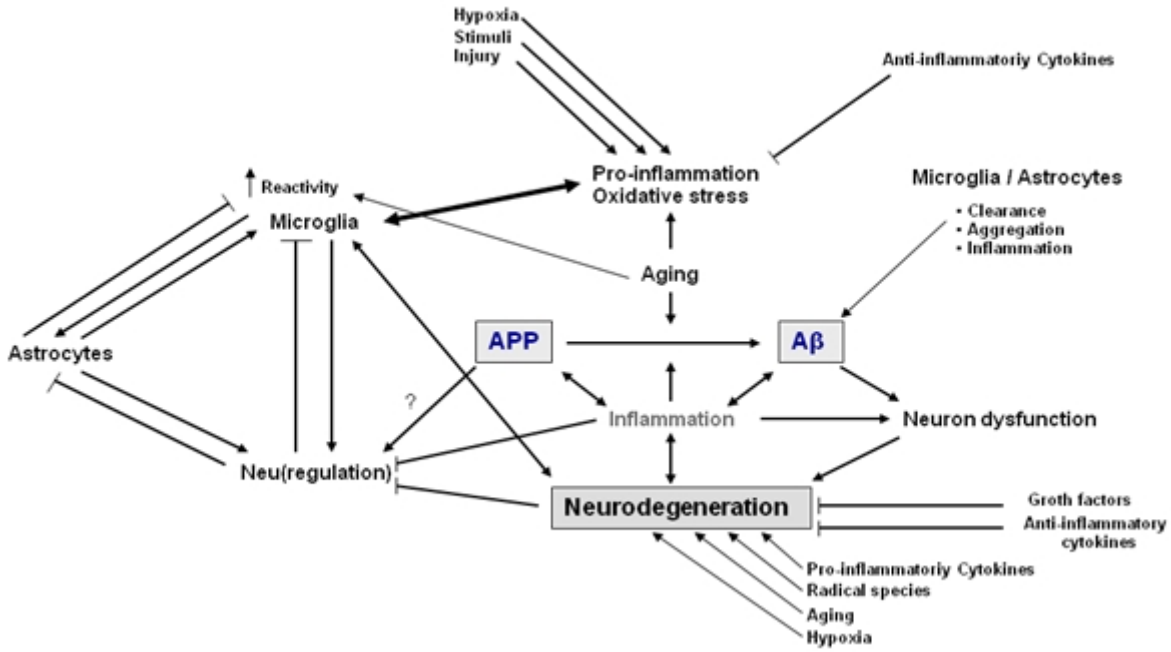
Dementia is a very heterogeneous disease. Multiple diagnostic entities exist, of which Alzheimer’s disease (AD) is the most common. Other frequently occurring dementias are Vascular Dementia (e.g. multi-infarct dementia, Binswanger’s dementia), Lewy Body Dementia (e.g. Parkinson’s disease, diffuse Lewy Body Dementia, and Lewy Body variant of AD) and other forms (e.g. Frontotemporal Lobar Degeneration, Creutzfeld-Jacob Disease, Corticobasale Degeneration, potentially reversible dementias).

Each dementia has its own clinical correlate, its own aetiology and pathogenesis, which is multifactorial. In AD the following hypothesis are discussed and intensively investigated [54-61]:

- cholinergic dysfunction
- beta-amyloid toxicity
- tau-hyperphosphorilation
- oxidative damage
- mitochondrial dysfunction
- synaptic dysfunction
- inflammation reactions through glia, cytotoxic activation
- deranged glucose metabolism
- deranged lipid metabolism
- proteomic dysfunction
- calcium dysregulation
- polysaccharide deposits

An overview of these pathogenic interactions gives Figure 13. One key finding is that many degenerative processes are mediated through inflammation. Inflammation may accelerate and therefore constitute the degradation of Amyloid Precursor Protein to Aβ and may induce many other neuropathological alterations of AD.

FIGURE 13: PATHOGENESIS OF ALZHEIMER'S DISEASE ACCORDING TO [60]



APP: Amyloid Precursor Protein, Aβ: beta-amyloid

TREATMENT OPTIONS

The three main symptoms of AD are cognitive impairment, non-cognitive impairments - also known as behavioural and psychological symptoms of dementia (BPSD) - and impairment of daily living activities. Cognitive decline was the primary target in investigating drugs for dementia. BPSD and impairment of daily living activities have long been neglected in research.

There are different therapeutic approaches targeting each main symptom. Pharmacological treatment approaches only exist for two hypotheses of the complex pathogenesis of AD and primarily target cognitive decline: cholinergic dysfunction and cytotoxicity.

GENERAL TREATMENT RECOMMENDATIONS

Acetylcholine Esterase Inhibitors (AChEI), such as donepezil, rivastigmine and galantamine inhibit the acetylcholine esterase in the synaptic gap, resulting in higher

acetylcholine levels. Higher levels of acetylcholine should improve cognitive functioning. In clinical trials they have shown to modulate the course of AD in the sense that cognitive decline has been delayed for about one year [62]. Galantamine additionally modifies psychotic symptoms [63, 64]. AChEI are approved for early and middle-stage dementia. Common side effects are gastrointestinal symptoms such as nausea, vomiting or diarrhoea and symptoms of the central nervous system like dizziness, confusion, insomnia or fatigue.

Memantine is an NMDA receptor modulator. It lowers the synaptic concentration of glutamate in neurons. Chronically elevated synaptic glutamate levels, as in AD, reduce neuronal functioning and lead to neuronal death. Furthermore, memantine lowers the tau-hyperphosphorilation. Memantine is approved for late stage dementia only. Common side effects are dizziness, agitation, fatigue and nausea. The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWIG) evaluated the effect of memantine on cognition in AD patients and certified its benefits [65]. There are indicators of a beneficial influence of memantine in AD with regard to daily living activities [65].

GUIDELINES FOR ANTI-DEMENTIVE DRUGS

According to the German S3 Guideline “Dementias” [66] and the dementia guideline of the European Federation of Neurological Societies (EFNS) [67] acetylcholinesterase inhibitors (AChEIs) are recommended for mild to moderate Alzheimer and mixed dementia. Memantine is recommended for moderate to severe Alzheimer and mixed dementia.

The treatment of vascular dementia with AChEIs or memantine lacks substantiation and is thus not approved by the S3 Guideline. The EFNS guideline regards donepezil as a treatment option.

Pharmacologic treatment of mild to moderate Parkinson disease dementia and Lewy Body dementia with rivastigmine is effective and therefore recommended by the S3 guideline. The EFNS guideline uses the terms “can be considered” in relation to AChEIs.

NON-PHARMACOLOGICAL INTERVENTIONS

Apart from pharmacologic treatment approaches there are **psychosocial interventions**. Examples of psychosocial interventions are cognitive training, occupational therapy or physical activity. Studies in this field often have small numbers of participants, very heterogeneous outcomes and methodological deficits [66].

Cognitive training can be sub-divided into compensatory and restorative strategies and reminiscence therapy. “Compensatory strategies aim to teach new ways of performing cognitive tasks by ‘working around’ cognitive deficits” and “restorative strategies attempt to improve functioning in specific domains with the ultimate goal of returning functioning in those domains to premorbid levels” [68]. A Cochrane Review could find neither benefits nor harm through cognitive training [69], whereas a meta-analysis by Sitzer et al. found benefits for cognitive training [68]. The effect sizes for restorative strategies were higher than for compensatory strategies (0.54 vs. 0.36). The analysis of the IQWiG concludes some benefit with cognitive training [70]. Reminiscence therapy deals with the individual history of a patient. A Cochrane review found significant positive results for cognition and mood of the patient and significant less strain for the caregiver [71].

Occupational therapy is an intervention that targets the maintenance of daily living activities and an improvement in the quality of living in individual everyday life. Only few studies exist with small numbers of participants and heterogeneous endpoints. A report by the German Institute for Medical Documentation and Information (Deutsches Institut für Medizinische Dokumentation und Information, DIMDI) analysed different nursing concepts and could not find evidence for occupational therapy and others (e.g. validation, relaxation, sensory stimulation) on the basis of current study results [72].

Physical activity is a supportive intervention with the aim to slow down cognitive decline. Yet there is not enough evidence for clear recommendations, as a Cochrane review suggests [73].

TREATMENT OF BPSD

Antipsychotics are commonly used to treat BPSD. They reduce thinking and perception disorders, anxiety, tension and agitation. But they do not influence consciousness and intellectual abilities in patients with psychotic disorders. Antipsychotics can be classified to their chemical structure (e.g. butyrophenones), antipsychotic potency or how they act. Antipsychotics with a high potency usually have in low or medium dosages an antipsychotic effect without sedating the patient. Low potency antipsychotics have primarily sedating properties in low to medium dosages with only minor antipsychotic properties.

All antipsychotics act as an antagonist on dopamin-2 (D2) receptors. The antipsychotic properties correlate positively with the affinity towards the D2 receptors. The second generation antipsychotics predominantly have an antagonistic effect on serotonine-2 (5HT-2) receptors as well. Atypical antipsychotics have replaced conventional ones in many fields due to their different side-effect profile. They are called atypical, because they cause a typical side-effect, extrapyramidal symptoms (EPS) to a lower extent.

Antipsychotics are originally used for the treatment of schizophrenia, but also for psychotic depression and mania. Schizophrenia is definitely the most important indication for the use of antipsychotics. Antipsychotic therapy is recommended to be implemented upon the first manifestations of acute symptoms of schizophrenia [74]. Antipsychotics are also approved for relapse prevention of schizophrenia and mania. Antipsychotic agents have potential side effects like vegetative disorders such as a decrease in blood pressure, orthostatic hypotension, changes in the electrocardiogram (especially QT prolongation), sweating, dry mouth, constipation, impotence, ejaculation disorders and anorgasmia [75]. Further they can cause weight gain and a metabolic syndrome, as well as EPS such as parkinsonism, akathisia, somnolence, dyskinesia and agitation. For patients with Parkinson dementia or Lewy body dementia first, and many second, generation antipsychotics are contraindicated, because they worsen the symptoms of Parkinson disease and cause attacks of somnolence. Antipsychotics that can be considered for these disorders are clozapine and, although less-well substantiated, quetiapine.

GUIDELINES FOR TREATMENT OF BPSD

BPSD can be treated with psychosocial intervention or psychotropics. The German S3 guideline recommends the analysis of psychosocial findings prior to administration of psychotropics such as antipsychotics, benzodiazepines, anti-depressants or anti-epileptics. Should the psychosocial intervention fail, be insufficient or not available, then this is an indication for a pharmacological intervention [66]. Behavioural and psychological symptoms of dementia are clusters of various symptoms. For each symptom cluster the German S3 guideline gives specific therapeutic suggestions. The cluster “affective disorders” includes depression and anxiety. Antidepressants, with the exception of tricyclic antidepressants, are recommended for depression. For anxiety there is no evidence-based pharmacologic treatment. Another cluster is “hyperactivity”, including agitation and aggressive behaviour. Haloperidol is not recommended for agitation, possibly for aggressiveness. Risperidone is effective in agitation and aggressive behaviour, as is aripiprazole. Olanzapine is not approved. Apart from antipsychotics, anticonvulsive drugs such as carbamazepine are recommended. There is weak evidence in favour of the antidepressant citalopram. However, implementation in the case of agitation might be justified. For the cluster “psychotic symptoms” the S3 guideline only suggests the SGAs risperidone and aripiprazole.

In summary, the S3 guideline only recommends the two SGAs risperidone and aripiprazole. In the case of olanzapine the data are too heterogeneous and its secondary anticholinergic action is unfavourable.

CRITICAL REVIEW ON THE ROLE OF ANTIPSYCHOTICS IN THE TREATMENT OF BPSD

In 2005 and 2006 the Food and Drug Administration (FDA) published some “dear doctor” letters, respectively black-box warnings, in which they “determined that the treatment of behavioural disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications is associated with increased mortality” [9] based on a meta-analysis by Schneider [76]. Additionally, “Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials with risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with a placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis” [77]. It is unclear to which study the FDA refers in the full prescribing information, but a meta-analytical summery revealed an significant increased risk for CVAE under risperidone treatment compared to placebo (OR: 3,43; CI: 1,60 – 7,32; p = 0,001) [6]. In Germany risperidone is approved for the treatment (up to six weeks) of persistent aggression in patients with mild to moderate Alzheimer’s dementia in the following cases: no response to non-pharmalogical interventions and a risk of endangerment to self and others [78].

Herrmann asked in 2005 “Do atypical antipsychotics cause stroke?” and answered his question as followed: “Results … suggested higher rates of CVAEs in drug treated subjects” [79]. Further research confirmed these findings: Kleijer et al. delivered a more sophisticated illustration: they found in a case control study that current and recent exposure to antipsychotics were associated with an increased risk of CVAE compared with non-users (OR: 1,7; CI: 1,4 – 2,2). The OR is elevated for a history of use for less than one week (OR: 9,9; CI: 5,7 – 17,2). The risk decreases with time and is comparable to non-users after 3 months of use (OR: 1,0; CI: 0,7 – 1,3). Cumulative exposure was not associated with an increase in risk. They conclude that the risk of CVAE in elderly and demented patients associated with antipsychotics is elevated especially during the first weeks of treatment. This risk decreases over time and is back at base level after 3 months of treatment; thus

chronic use is not associated with CVAE [80]. A review analyzing clinical trials and observational studies by Sacchetti and co-workers presents similar data [81]. All these results correspond, as the studies included in the meta-analysis by Schneider and colleagues, which grounded the FDA warnings, mostly have a maximal duration of 3 months [76].

The rate of death seems to be elevated under antipsychotic treatment. Schneider calculated in a meta-analysis an Odds Ratio (OR) for SGA alone of 1.54 (CI: 1,06 – 2,23; p = 0,02), which reflects an occurrence of 3,5% for SGA, respectively 2,3% for placebo [76]. Liperoti and colleagues performed a retrospective cohort study, in which they found that the rate of death for users of FGA (hazard ratio [HR]: 1,26; 95% CI: 1,13 – 1,42) was higher than in SGA-users [82]. A two year prospective study in nursing homes and hospitals established that neither the use of atypical antipsychotics nor the use of typical ones increased mortality or hospital admissions [83]. As results from different type of studies are heterogeneous, there is a need to orientate on the highest level of evidence, which is provided by double blind randomised trials, and, of course, meta-analysis. Thus, in view of the various and frequent side-effects, respectively adverse events, treatment of BPSD with antipsychotics, as a mainstay of pharmacological therapy, had to be re-evaluated. Bullock, for example, suggested that “international guidelines are now required that direct prescribers in the appropriate use of alternative therapies for BPSD. AChEIs, particularly rivastigmine, can delay the onset and reduce the severity of neuropsychiatric symptoms in dementia, and decrease the requirement for antipsychotic and other psychotropic medications” [8].

In their work Jeste and colleagues mention, that “because of the recent black-box warnings about strokes and mortality with atypical antipsychotics …, some clinicians have begun to switch to the older typical antipsychotic agents” [84]. However, this is actually regarded critically by Hermann and Lanctot. Their “review suggests that there is no rationale to revert to the use of typical antipsychotics for BPSD given that their use is clearly associated with increased EPS, probably similar rates of cerebrovascular adverse events and mortality, and worsened cognition” [10]. Many experts still see the need for antipsychotics even though with a more stringent indication, e.g. “when severe and distressing symptoms are occurring...and when the

affected individual or others are at risk" [85]. Meeks and Jeste give the advice that "when treatment becomes necessary, atypical antipsychotics are one of several off-label treatment options but, if chosen, should be used judiciously in the context of shared-decision making, close monitoring, and minimization of dose/treatment duration" [86].

In conclusion: BPSD needs to be treated and effective treatment options are rare. Therefore, clinicians cannot abandon antipsychotics. Their application is off-label and their use should be minimized: Only as much as necessary and only as long as needed.

AIMS, HYPOTHESIS AND METHODS

The question we asked was: Are first generation antipsychotics superior to second generation ones, or vice versa? The appropriate way of answering this question is by setting up a study, or, if enough studies exist, by performing a meta-analysis. Systematic reviews and meta-analysis are considered important instruments in the evaluation of medical treatments and are rated in guidelines with the highest grade of evidence.

Approximately two to three million articles are published in about 10,000 medical journals every year [87]. A general practitioner, wishing to keep up to date with the developments in this field, would have to read 19 articles per day [88]. There are at least 150 randomised controlled trials for the treatment of schizophrenia, comparing SGAs and FGAs. As it is so extremely difficult to maintain an overview over this incredible flood of studies, meta-analysis has developed into an essential tool for researchers and clinicians [89].

What other options do clinicians and researchers have? They could view individual studies and base their treatment decision on these results. It is however unclear which of the 150 schizophrenia trials comparing atypical and conventionals to select. The random choice of any of the 150 studies could lead to a biased treatment decision. In consequence, the patient might not receive the optimal therapy. In such cases, the methodology of choice is a meta-analysis as it includes an extensive search for papers in several databases and hand search of journals. Only studies fulfilling a certain pre-defined standard will be included in the analysis. Furthermore, publication biases can be detected. Studies with negative results are less likely to be published. This publication bias can be detected with a funnel plot [19].

The non-observance of possible important differences across studies is the most popular criticism of meta-analysis. This is also known as the problem of comparing apples and oranges. Gene Glass, one of the pioneers of this method, said that this is alright as long as you want to give a statement about fruit [90]. Of course, studies included in meta-analysis do differ and the question of inclusion is always an individual one. But it should be not forgotten, that meta-analyses always address broader questions than individual studies [91]. Another point of criticism is that meta-

analysis is so complicated, that mistakes are inevitable and reviewers are unable to detect all of these, as verbalized by John C. Bailar [92]. Many meta-analyses do indeed contain mistakes. But these are more a problem of the persons performing a meta-analysis than a problem of the method itself. Other studies contain mistakes and errors as well. Bailar “still prefer(s) conventional narrative reviews of the literature, a type of summary familiar to readers of the countless review articles on important medical issues” [92]. A conventional or narrative review is subject to the same biases as a systematic review and meta-analysis. A systematic review will assess the results of an extensive search according to several quality standards. In a narrative review with no systematic approach, study selection might be arbitrary. In meta-analysis the focus is on the effect size, in narrative reviews on the p-value. Even small effect sizes can be significant, but have no clinical relevance. On the other hand, a large effect size is not significant because it is underpowered. Furthermore, a narrative review will not be able to assess the pattern of dispersion and the relationship to other variables, whereas meta-analysis provides tools to do so [91].

For illustration purpose, the principles of a narrative review are briefly described. For a narrative review we would probably include some studies included in this meta-analysis and some of the excluded studies due to methodological reasons. We might practically include the following studies [93-99]. Two of them were of a single blind design [93, 96] and five were open-label studies [94, 95, 97-99]. The duration of the studies varied from 56 days to 12 months and the number of participants from eight to 338. Efficacy was measured with the same scores as in our meta-analysis (CMAI, NPI, BEHAVE-AD and BPRS) and, if multiple scores were presented, the same order of choice as in the meta-analysis would be applied. A result would be considered significant with a p-value less the 0,05 in the analysis from baseline to endpoint. The results of the efficacy analysis for each individual study shows nine significant improvements under antipsychotic treatment and two non-significant results which is a ratio of 9:2. A ratio of 9:2 might be tempting for the reader to suppose a great advantage of antipsychotic treatment compared to placebo. However, there is and there can be no statement of the treatment effect itself. Regarding the fact that

results can be highly significant but with only a marginal effect far from being clinically relevant, the interpretation of narrative reviews calls for a degree of caution.

To address the intensity of treatment or side-effects meta-analyses provide effect sizes as results. These effects can be quantified: according to Cohen an effect size of 0,2 is small, 0,5 medium and 0,8 large [100].This systematic review and meta-analysis claim to answer the question as to which antipsychotic class is superior. As explained above the studies included - and thus this analysis - are subject to several limitations. This means that all the results have to be regarded in a certain context.

RESULTS

EFFICACY

This is the first meta-analysis to compare first and second generation antipsychotics in the treatment of BPSD. In the pooled efficacy analysis there is a small effect favouring antipsychotic treatments for FGA and SGA. FGAs would seem to be superior. But the studies of the FGA group were older, with a smaller number of participants and of poorer quality. There are randomised studies (not included for missing placebo control) comparing SGA and FGA (haloperidol) directly [101, 102]. These did not find differences in efficacy or side effects with one exception: significant more EPS measured on the Simpson Angus Scale in patients treated with haloperidol [101].

The efficacy analysis of single antipsychotics was very inhomogeneous. There were small to moderate effects for most of the antipsychotics, which were rarely significant. Treatment of BPSD with the FGAs pimozide and thioridazine proved not to be superior to placebo. For SGAs these results are consistent to other meta-analysis [6, 103]. These only analysed SGAs. Davidson and co-workers only included three studies in their analysis [103]. Schneider differentiated in his analysis for each SGA between the scales (e.g. BPRS, CMAI, NPI): for most of the antipsychotics, results are consistent independent of the applied scale [6]. In this meta-analysis, we found with exception of two antipsychotics treatment effects in BPSD. These effects are rather small, but regarding that study patients are probably given more attention in general, might limit the observed treatment efficacy compared to placebo. In daily routine this effect might be larger as naturalistic studies suggest (see below). Nevertheless treatment options, especially in acute BPSD, are rare. Benzodiazepines can also be used but elevate the risk of fall and associated injuries and hospital admission [104] as well as they increase the risk of delirium in the elderly [105]. Another alternative could be anticonvulsants like topiramate. In a study by Mowla and Pani topiramate proved to have a comparable efficacy to risperidone in BPSD [106].

EFFECTIVENESS

Effectiveness and tolerability seems to be comparable between first and second generation antipsychotics in this meta-analysis. The reporting of effectiveness and tolerability was very incomplete and highly varies between the studies (see table 2). Mostly older studies, commonly investigating FGA are lacking these data. But also younger studies suffer from under-reporting of these items.

The global drop-outs were equal for all groups here (RR = 1,005; p = 0,833). Other meta-analyses confirm this finding [76, 103]. Drop-out rates due to specific reasons like inefficacy and adverse events have not been investigated by others so far. We found drop-outs due to inefficacy to be slightly higher for placebo (RR = 0,702; p = 0,004) and, due to adverse events to be increased for antipsychotics (RR = 1,537; p = 0,000). These effectiveness results indirectly mirror the efficacy and tolerability results of antipsychotic treatment in dementia, as inefficacy leading to an advanced drop-out of the study is more often detected in placebo. And as expected there were more severe adverse events leading to an advanced cessation for study participants belonging to the verum group.

TOLERABILITY

Our tolerability analysis revealed mostly no difference between FGA and SGA, but between antipsychotics and placebo. Under antipsychotic treatment there was less agitation compared to placebo (RR = 0,773; p = 0,012). Agitation can be one symptom of BPSD and therefore a reduction in agitation is preferable and expected under antipsychotic treatment.

As agitation is reduced under antipsychotic treatment, the risk for somnolence raises (RR = 2,7; p < 0,001) in our pooled analysis of all antipsychotics. That result is consistent with former meta-analytic investigations on SGAs [6, 103]. With focus on FGA a non-significant elevated risk for somnolence is seen under haloperidol treatment (RR = 3,0; p = 0,07), which might be due to high doses. Elderly patients react very sensitive on antipsychotics. Doses of 0,25 mg are recommended [107]. The mean daily haloperidol dosage was 1,2 mg [44], 1,9 mg [47], and 3,53 mg [30] in

the studies included to this analysis. Estimating three to four daily doses, all studies used higher doses than recommended. There was only one trial investigating somnolence under tiapride treatment. Although it belongs to lower potency antipsychotics it has only a minor sedating effect. This fact is mirrored in this meta-analysis: the risk for somnolence was equal between tiapride and placebo (RR = 1,01; p = 0,98).

The risk for accidental injuries is in this meta-analysis almost the same for placebo and antipsychotics (RR = 0,973; p = 0,691). There is only a marginal difference between FGA and SGA (FGA vs. PBO: RR = 1,078; p = 0,642; SGA vs. PBO: RR = 0,964; p = 0,592) which is compared to placebo far from statistical significance. The meta-analysis by Schneider and colleagues investigating SGA confirms these results [6].

Our analysis for the risk of death under antipsychotic treatment vs. placebo treatment was very heterogeneous between the individual studies. It was irrelevant, if the antipsychotic belonged to first or second generation. The pooled individual drug results show a higher probability of death under antipsychotic treatment, but without statistical significance. In case of all trials pooled, there is an elevated risk as well with a statistical significance (RR = 1,564, p = 0,039). Comparing FGA vs. placebo and SGA vs. placebo there are only minor differences without reaching the level of significance (FGA vs. PBO: RR = 1,435; p = 0,784; SGA vs. PBO: RR = 1,52; p = 0,059). The meta-analysis entitled “Risk of death with atypical antipsychotic drug treatment for dementia” showed similar results [76]. The authors calculated an odds ratio (OR) to measure the risk of death. They found an OR of 1,54 (p = 0,02), which means a 1,54 times higher chance for death under antipsychotic treatment than under placebo. A remaining point of criticism is that for effectiveness analysis the RR is the more intuitive instrument.

The occurrence of extrapyramidal symptoms did not differ statistically significant in our overall analysis (antipsychotics vs. placebo). Only in the parkinsonism overall analysis there is a trend for a higher risk for antipsychotic treatment (RR = 1,679; p = 0,053). Analysis of the Simpson Angus Scale reveals a small effect worsening for the verum group (Hedges’s g = 0,201; p = 0,005). Most of the FGA studies did not provide data on EPS. Where provided the subgroup analysis mirrors the typical side-

effects of e.g. Haloperidol (AIMS: Hedges's g = 0,249; p = 0,095; SAS: Hedges's g = 0,825; p < 0,001). Regarding dichotomous EPS data collection there is an elevated risk for some FGAs compared to placebo (haloperidol: RR = 2,02; p < 0,001; loxapine: RR = 2,75; p = 0,04). Another meta-analysis focussing on SGA only found an odds ratio of 1,51 (p = 0,0005) for extrapyramidal signs and symptoms [6]. Here again the odds ratio is the less intuitive and less appropriate statistical tool for assessing the risk of adverse events. With those data (13% EPS for SGA and 8% for PBO) a risk ratio of 1,625 can be calculated. We detected a risk ratio of 1,418, including FGA and more SGA studies. But still the results are consistent: there is an elevated risk for EPS under antipsychotic treatment for FGA and SGA.

COGNITION

The present analysis of cognitive abilities represented with the MMSE varied from 0 to -2,06 (absolute values) between the included studies. Meta-analytic calculations revealed a trend towards deterioration under antipsychotic treatment, compared to placebo (fixed effects model: Hedges's g = -0,101; p = 0,044; random effects model: Hedges's g = -0,066; p = 0,343). Based on heterogeneity, the random effects model seems to be appropriate. The displayed negative effect is neither strong nor statistically significant. The meta-analysis by Schneider and co-workers resulted in a statistically highly significant but small effect (weighted mean difference = 0,73, p < 0,0001) in MMSE worsening for SGAs [6]. This work included four SGA studies less than we did. Their corresponding heterogeneity analysis was not statistically significant. So they probably used a fixed effects model. In general there was a strong underreporting of the MMSE at the endpoint of the study or the mean change in MMSE, respectively.

It is questionable whether these negative effects on cognition are so marginal in clinical reality. Sakurai and co-workers found out that in patients with schizophrenia D2-receptor occupancy higher than 80% was associated with impairment in cognitive functioning and vigilance [108]. In healthy subjects there is also evidence that a single dose of haloperidol [109] as well as the administration of haloperidol up to

seven days can cause a decline in cognitive functioning [110-112], but also aripiprazole [112].

In RCTs there are highly selected samples with a daily schedule and good care. A cognitive decline was may be minimized. In a nursing home setting the cognitive decline of a dementia patient taking antipsychotics could be much worse. After two months of treatment of BPSD with risperidone in rural nursing homes, Ellingrod found a cognitive decline of 2,27 (Standard Deviation 3,13) in the MMSE, which was significant [113]. In the olanzapine group of the same study, the loss in the MMSE was 1,38 (Standard Deviation 2,77). A limitation of this study is admittedly the very small sample size of 19 patients (eleven patients taking risperidone, eight taking olanzapine). A single-blind pilot study on haloperidol for treating BPSD in AD by Devanand shows an interesting development on the MMSE [93]. For the first four weeks the patients receive placebo, than haloperidol for eight weeks and then again placebo for four weeks. At the end of the first placebo phase the MMSE was 23,3 (SD = 16,4). At the end of the haloperidol phase it decreased to 18,1 (SD = 15,3). At the end of the last placebo phase it increased to a value of 20,1 (SD = 14,4). This study is limited to its very small number of participants (n = 9). In direct FGA vs. SGA competition studies the MMSE mean change values between haloperidol (-0,15; SD = N/A) and risperidone (-0,42; SD = N/A) [101], or haloperidol (-0,13, SD = 3,54) and olanzapine (0,53, SD = 3,54) [102] differs only slightly. We can confirm these results in our meta-analysis. But we only included two trials investigating FGAs (both haloperidol) due to underreporting. The study entitled “Olanzapine does not enhance cognition in non-agitated and non-psychotic patients with mild to moderate Alzheimer’s dementia” was conducted on outpatients [96]. 178 patients were randomised to olanzapine and 90 to placebo. After 26 weeks the MMSE worsened by 2.06 points (SE = 0.29; within-group p-value < 0.001) in the olanzapine group and by 0.57 (SE = 0.38; within-group p-value = 0.139) in the placebo group. The p-value between both groups was 0.002. A significant worsening of cognition was also seen in the ADAS-Cog.

The usage of MMSE assessing the cognitive course in dementia is questionable. There are more specific and sophisticated tools like e.g. ADAS-Cog. But if any cognitive course was reported, it was MMSE. Only very few studies assessed or

published ADAS-Cog additionally. Summing up, there is a treatment effect of antipsychotics in BPSD with considerable side-effects and serious adverse events like EPS or death. The observed small effect of higher cognitive decline in the treatment groups could be quite larger in real life. In the light of very high prescription rates of antipsychotics in dementia patients [114-116], current prescription manner has to be reconsidered.

LIMITATIONS AND CONCLUSION

The summarized effect is based on the data of included randomized controlled trials. These trials have strict and predefined exclusion criteria. This leads to a highly selected sample. Usually dementia patients are treated by primary care physicians, whereas many RCTs include patients who only have contact to psychiatric research centres [117]. In addition RCTs have a predefined treatment regimen. In daily clinical routine there are variations of the dosage depending on the patient's condition. Furthermore, patients in a study setting have a structured daily schedule, medical examinations and care. In a nursing home dementia patients do not often have these advantages. Nurses have less time per patient for care and a structured daily schedule is lacking. In this situation a larger benefit is described by some open label studies. One study took place in nursing homes [118], one in different medical centres [94], and two in outpatients [119, 120]. All four studies used risperidone. One study compared risperidone versus melperone [119]. All treatments led to an improvement in behavioural and psychological symptoms of dementia. In the study of Wancata general practitioners, care-givers and patients were asked via questionnaire about the efficacy of risperidone [118]. The results are impressive. According to the general practitioners, the efficacy is excellent in 53% of the patients and satisfactory in 44%. Care-givers share this view. Patients judge efficacy as excellent in 41% and as satisfactory in 54%. Kurz et al. also found only significant improvements in measured symptoms, like agitation, aggressiveness, disturbance of sleep-wake rhythm and others [120]. When regarding these optimistic results, the small sample sizes and the industrial sponsoring should not be forgotten. Nevertheless, there seems to be a measureable effect in treating BPSD with antipsychotics.

Another problem we are faced with is the varying quality of studies within the included randomized controlled trials. Older studies are lacking certain quality standards. Quality-based principles and methods were established in the nineties with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [121]. The aim of Good Clinical Practice (GCP) recommendations issued by the ICH was to define standards for the ethical, scientific and technical quality on drug substances, diagnosis and therapies. This concerns in particular the protection of patients in clinical trials, the authenticity

of data obtained and results and the establishment of responsibilities associated with clinical drug trials [122].

We included in this meta-analysis 17 RCTs investigating only SGA and 8 RCTs investigating only FGA. The 17 RCTs on SGA included an average of 303 participants per study, whereas the 8 RCTs on FGA included an average of 85 participants per study. 15 SGA studies were published between 2000 and 2008, one in 1999 and one remains unpublished. 3 FGA studies were published in the eighties, one in 1998 and three between 2000 and 2002. So we assume the trials from the eighties and early nineties to have a different quality standard, which would not satisfy current standards. These are trials researching FGA only. What is also mentionable is the fact that mostly older FGA trials have in average considerably less participants than the SGA trials. They are probably lacking a power analysis.

Antipsychotics are the mainstay in the treatment of BPSD, especially in an acute onset of symptoms. According to the present analysis, there seems to be no relevant difference between first and second generation antipsychotics regarding efficacy, tolerability and side-effects. Open-label studies suggest that efficacy is probably higher in daily clinical routine than in randomised controlled trials. However, the use of antipsychotics should be minimized to an absolute necessary, in view of the elevated risk of death and stroke, as well as a possible acceleration of cognitive decline.

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PUBLICATIONS

Wolf A, Leucht S, Pajonk FGB. Antipsychotische Therapie von Störungen bei Demenz. Eine systematische Übersichtsarbeit und Meta-Analyse randomisierter, kontrollierter Studien. Poster presented at the DGPPN Congress 2010, Berlin 24. – 27.11.2010

Wolf A, Leucht S, Pajonk FGB. Führen Antipsychotika bei Dementen zu einer Minderung der kognitiven Funktion? Eine Metaanalyse randomisierter, Placebo kontrollierter Studien. Poster presented at the DGPPN Congress 2010, Berlin 24. – 27.11.2010

Wolf A, Leucht S, Pajonk FGB. Do antipsychotics lead to cognitive impairment in dementia? A Meta-analysis of randomised placebo-controlled trials. Acta Scandinavica Psychiatrica. (Under review)

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