Qualitätssicherung in der Pharmakotherapie der Schizophrenie

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LVR Symposium 2015:
Qualität in der Psychiatrie –
Messung, Steuerung, Optimierung
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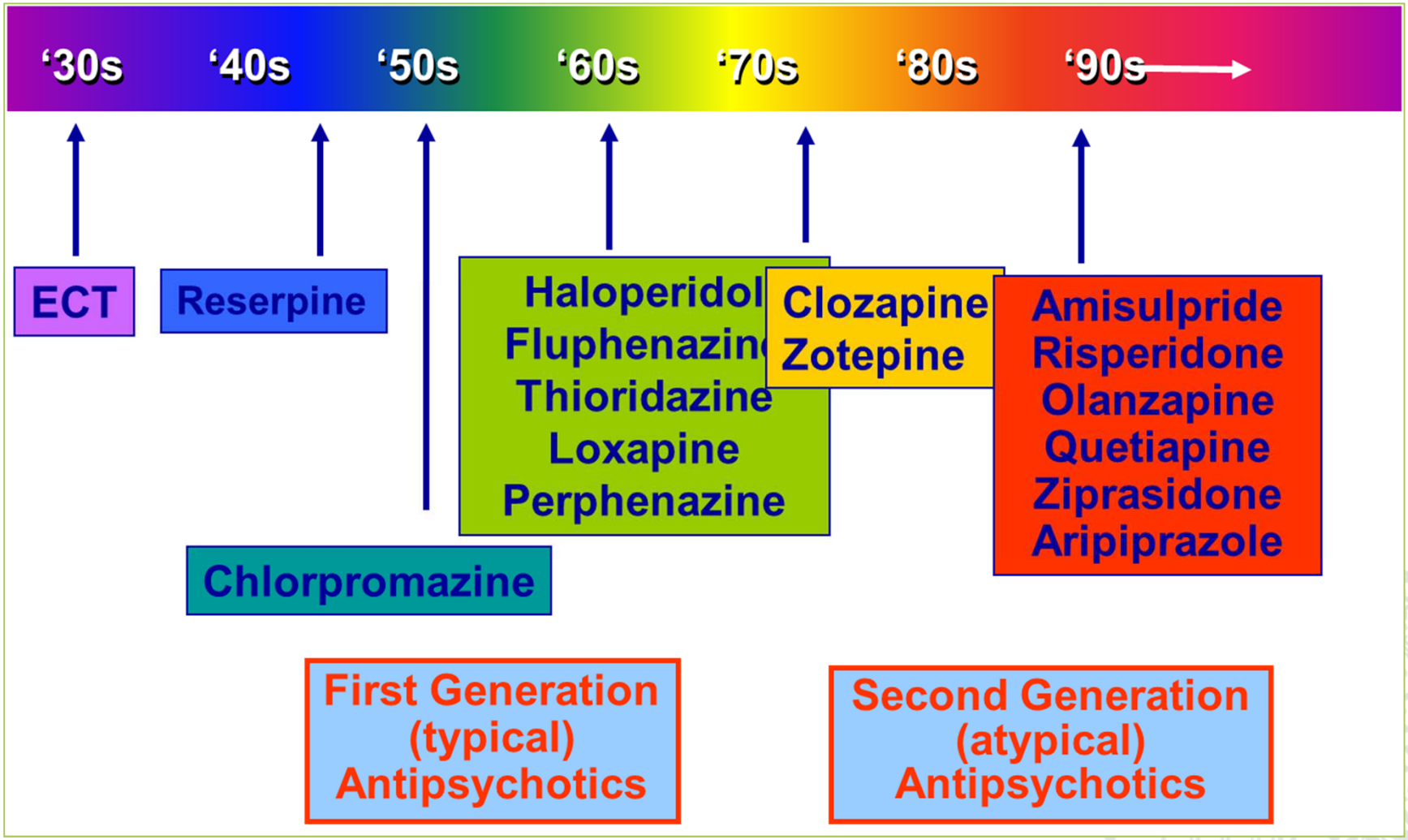
Qualitätssicherung über Leitlinien: Beispiel WFSBP Leitlinie

Qualitätssicherung über Messung der Wirksamkeit
- **Was?**
- **Wieviel?**
- **Wie lange bis zum Wechsel?**
- **Kombiniert?**
- **Wie lange insgesamt?**

Qualitätssicherung über Messung der Nebenwirkungen
- **Motorik**
- **Metabolik**
- **Zerebral**

Messung der Verhaltensänderung jenseits der Psychopathologie
- **Neuropsychologie**
- **Funktion**

Die Entwicklung von antipsychotisch wirksamen Substanzen



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Qualitätssicherung über Leitlinien: Beispiel WFSBP Leitlinie

Qualitätssicherung über Leitlinien?

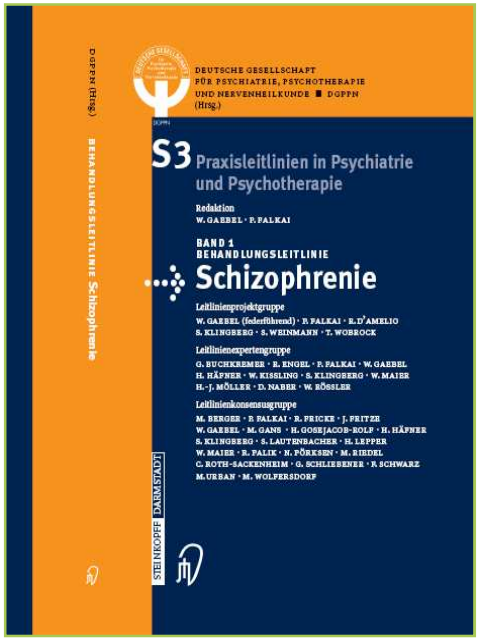
American Psychiatric Association Practice Guidelines

American Psychiatric Association (APA) practice guidelines provide evidence-based recommendations for the assessment and treatment of psychiatric disorders.

APA Steering Committee on Practice Guidelines | Statement of Intent | Copyright, Citation, and Disclaimer | Introduction

Practice Guideline for the Treatment of Patients With Schizophrenia Second Edition

GUIDELINE WATCH (SEPTEMBER 2009): PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH SCHIZOPHRENIA



The Schizophrenia Patient Outcomes Research Team (PORT): Updated Treatment Recommendations 2009

Julie Kreyenbuhl[1–3], Robert W. Buchanan[4], Faith B. Dickerson[5], and Lisa B. Dixon[2,3]

Schizophrenia Bulletin vol. 36 no. 1 pp. 94–103, 2010
doi:10.1093/schbul/sbp130
Advance Access publication on December 2, 2009

THE NICE GUIDELINE ON CORE INTERVENTIONS IN THE TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA IN ADULTS IN PRIMARY AND SECONDARY CARE

UPDATED EDITION

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders

Beispiel WFSBP Leitlinien

ALKOMIET HASAN[1], PETER FALKAI[1], THOMAS WOBROCK[1], JEFFREY LIEBERMAN[2], BIRTE GLENTHOJ[3], WAGNER F. GATTAZ[4], FLORENCE THIBAUT[5], HANS-JÜRGEN MÖLLER[6] & THE WFSBP TASK FORCE ON TREATMENT GUIDELINES FOR SCHIZOPHRENIA*

Part 1 **World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance**

The World Journal of Biological Psychiatry, 2012; 13: 318–378

Part 1 **World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects**

The World Journal of Biological Psychiatry, 2013; 14: 2–44

Part 3 Beginning of 2015: **Treatment of specific situations** – submitted; accepted for publication

WFSBP Leitlinien – Evidenzkategorien (I)

A	Full Evidence From Controlled Studies is based on: 2 or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) **and** 1 or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists). In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
B	Limited Positive Evidence From Controlled Studies is based on: 1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a"psychological placebo") **or** a randomized controlled comparison with a standard treatment without placebo control with a sample size suffi cient for a non-inferiority trial **and** no negative studies exist

WFSBP Leitlinien – Evidenzkategorien (II)

C	Evidence from Uncontrolled Studies or Case Reports/Expert Opinion
	C1 Uncontrolled Studies. Evidence is based on: 1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients) **or** a comparison with a reference drug with a sample size insufficient for a non-inferiority trial **and** no negative controlled studies exist
	C2 Case Reports. Evidence is based on: 1 or more positive case reports **And** no negative controlled studies exist
	C3 Evidence is based on the opinion of experts in the field or clinical experience
D	Inconsistent Results Positive RCTs are outweighed by an approximately equal number of negative studies
E	Negative Evidence The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a psychological placebo") or inferiority to comparator treatment
F	Lack of Evidence Adequate studies proving efficacy or non-efficacy are lacking.

WFSBP Leitlinien – Empfehlungsgrade

Recommendation grade	Based on
1	Category A evidence and good risk-benefit ratio
2	Category A evidence and moderate risk-benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

Qualitätssicherung über Messung/Bestimmung der Wirksamkeit

Auswahl von Antipsychotika bei mehrfach erkrankten Patienten mit einer Schizophrenie

Antipsychotic agent	Category of evidence[a]	Recommendation[b]
Amisulpride	A	1
Asenapine[1]	A	1/2
Aripiprazole	A	1
Clozapine[2]	A	1/2
Haloperidol	A	2
Iloperidone[1]	A	1/2
Olanzapine	A	1
Paliperidone[1]	A	1/2
Quetiapine	A	1
Risperidone	A	1
Sertindole[1,3]	A	1/2
Ziprasidone	A	1
Lurasidone	B	3
Zotepine	B	3

Hasan A et al. 2012: World J Biol Psychiatry; 13: 318-78

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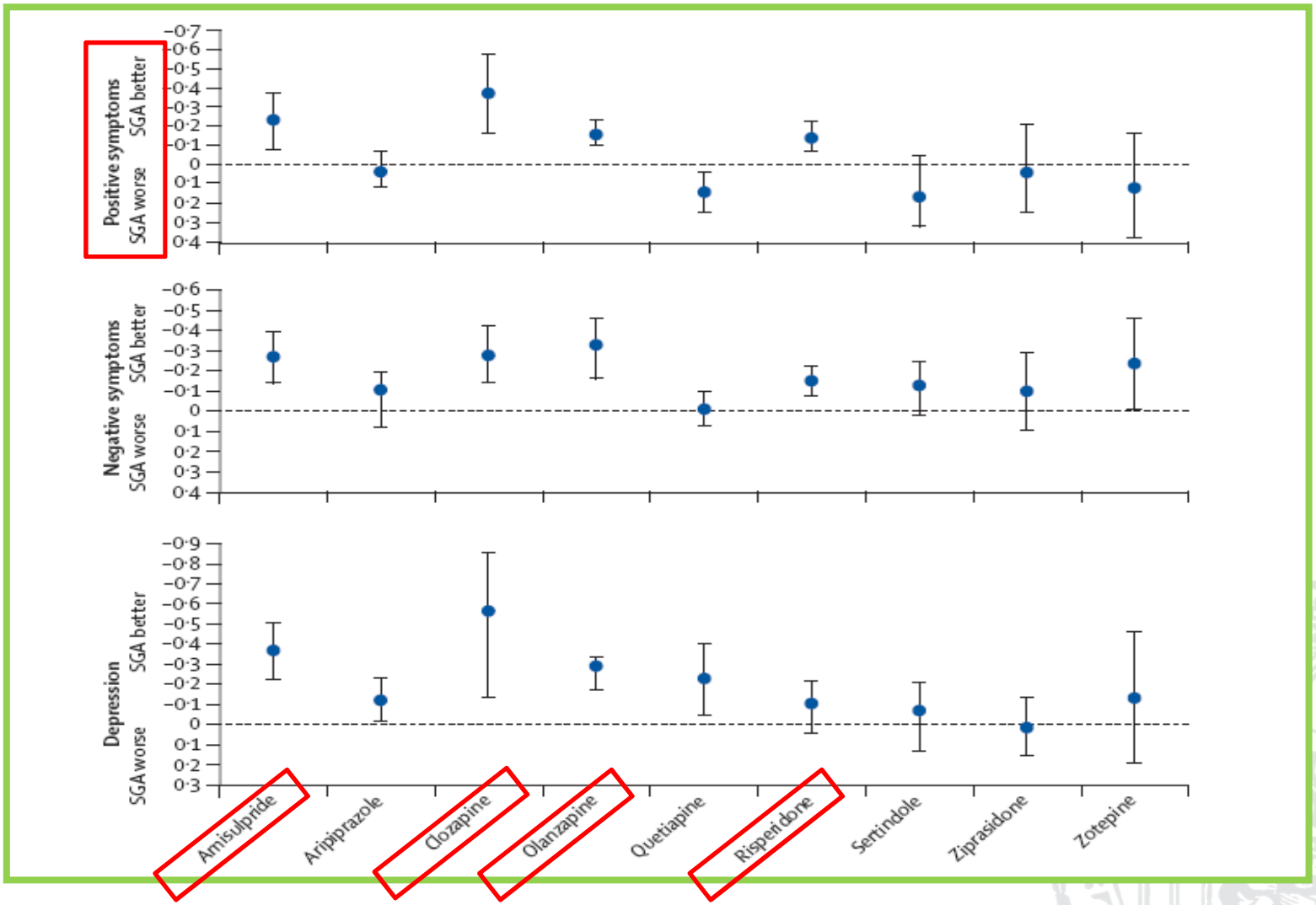
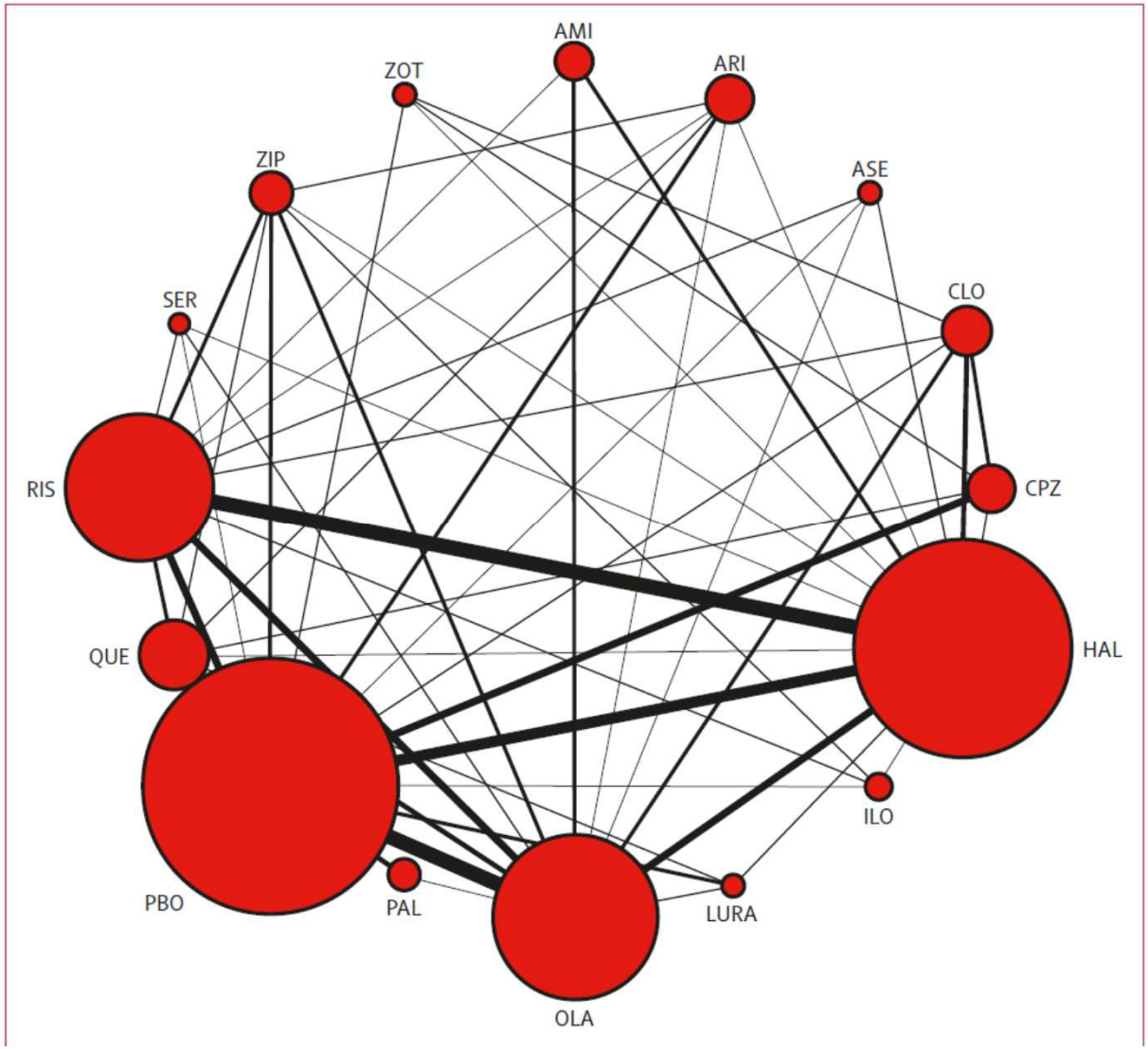
Auswahl von Antipsychotika nach Behandlungsdomänen (I)



Leucht et al. 2009: Lancet 3;373(9657):31-41

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Auswahl von Antipsychotika nach Behandlungsdomänen (II)



Network of treatment comparisons for overall efficacy

Leucht et al. 2013: Lancet 382(9896):951-62

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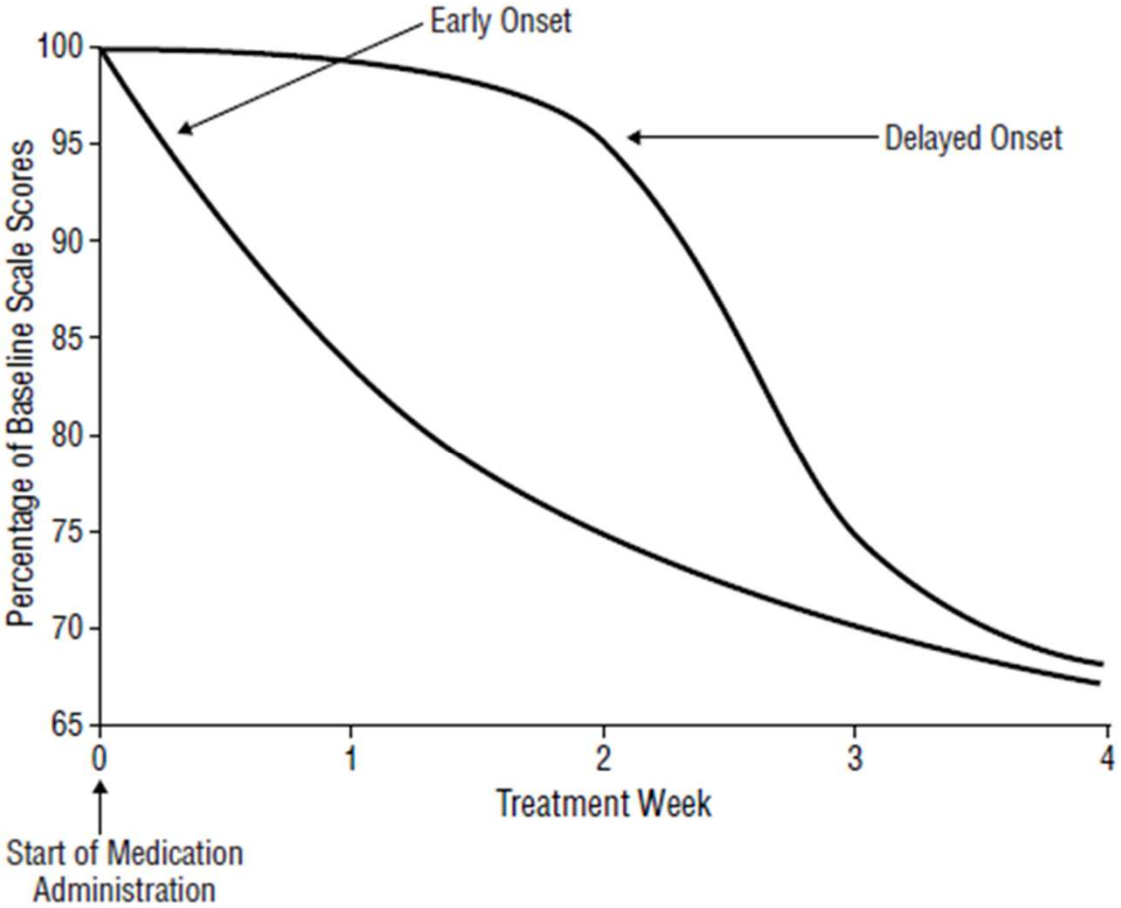
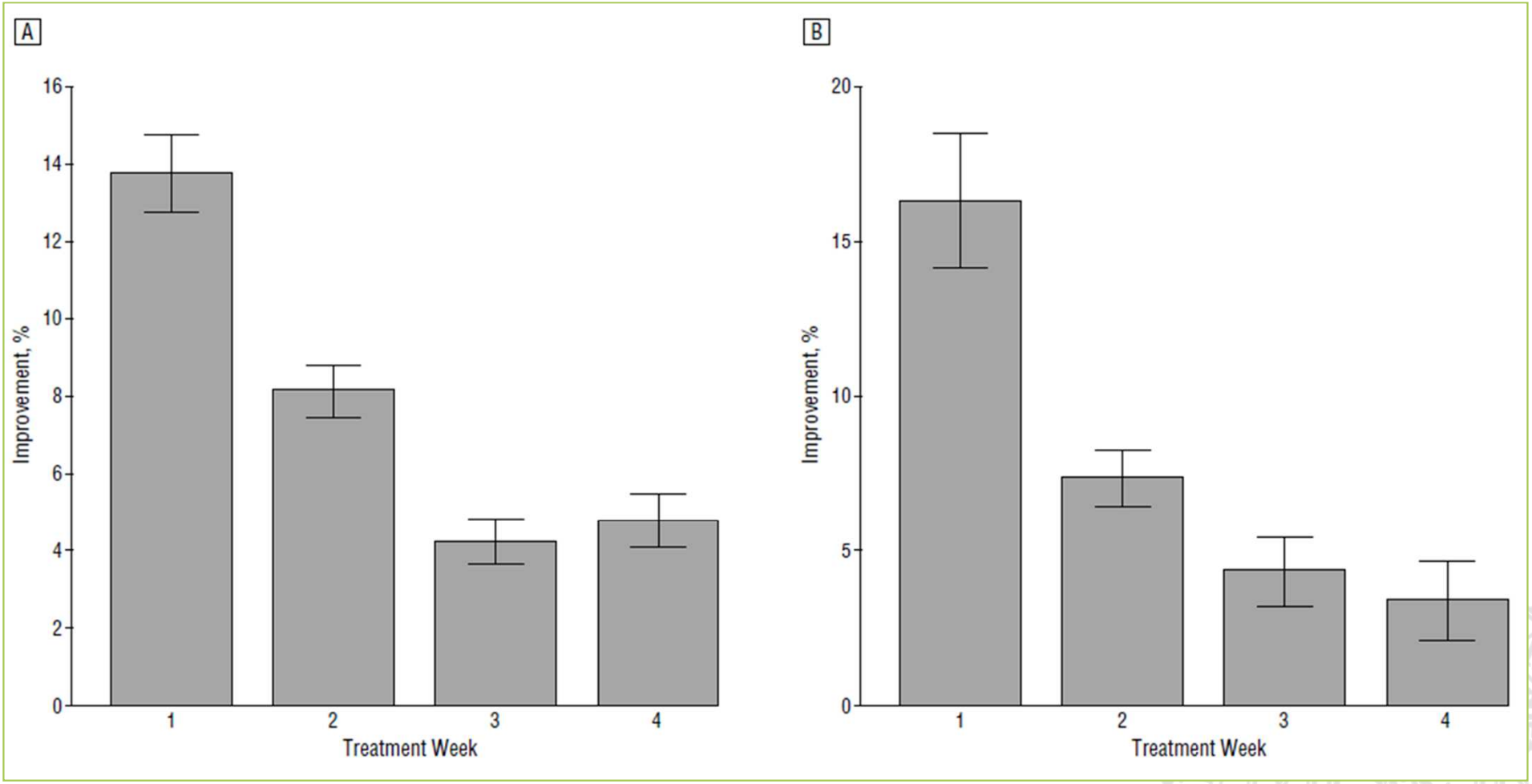
Behandlungsdauer mit einem Antipsychotikum: (1)-2 Wochen oder länger? (I)



Agid O et al. 2003: Arch Gen Psychiatry; 60: 1228-35

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Behandlungsdauer mit einem Antipsychotikum: (1)-2 Wochen oder länger? (II)



A: Mean overall clinical improvement (total score); (p<.001)
B: Mean change in core psychotic symptoms (p<.01)
P values represent the main effect of time. Error bars represent SE

Agid O et al. 2003: Arch Gen Psychiatry; 60: 1228-35

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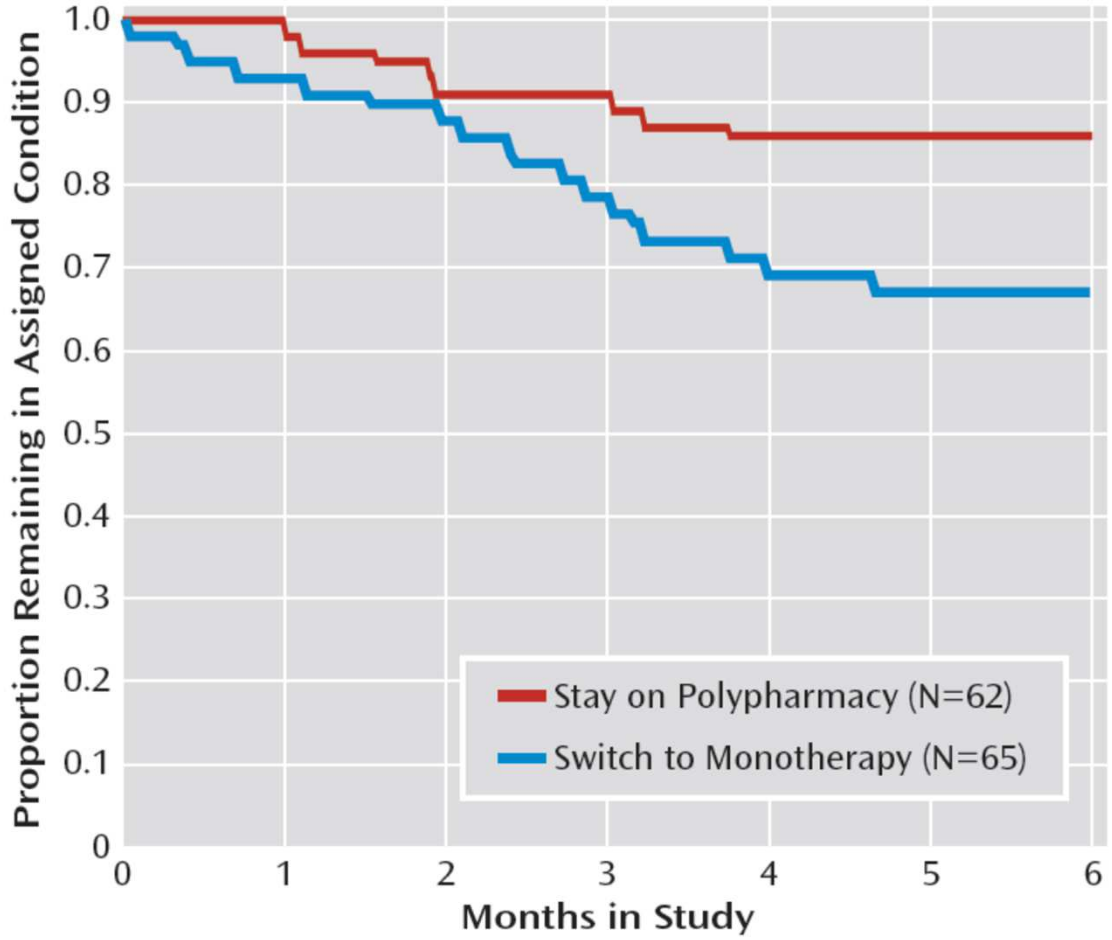
Kombination: Antipsychotikum+Antipsychotikum (1)



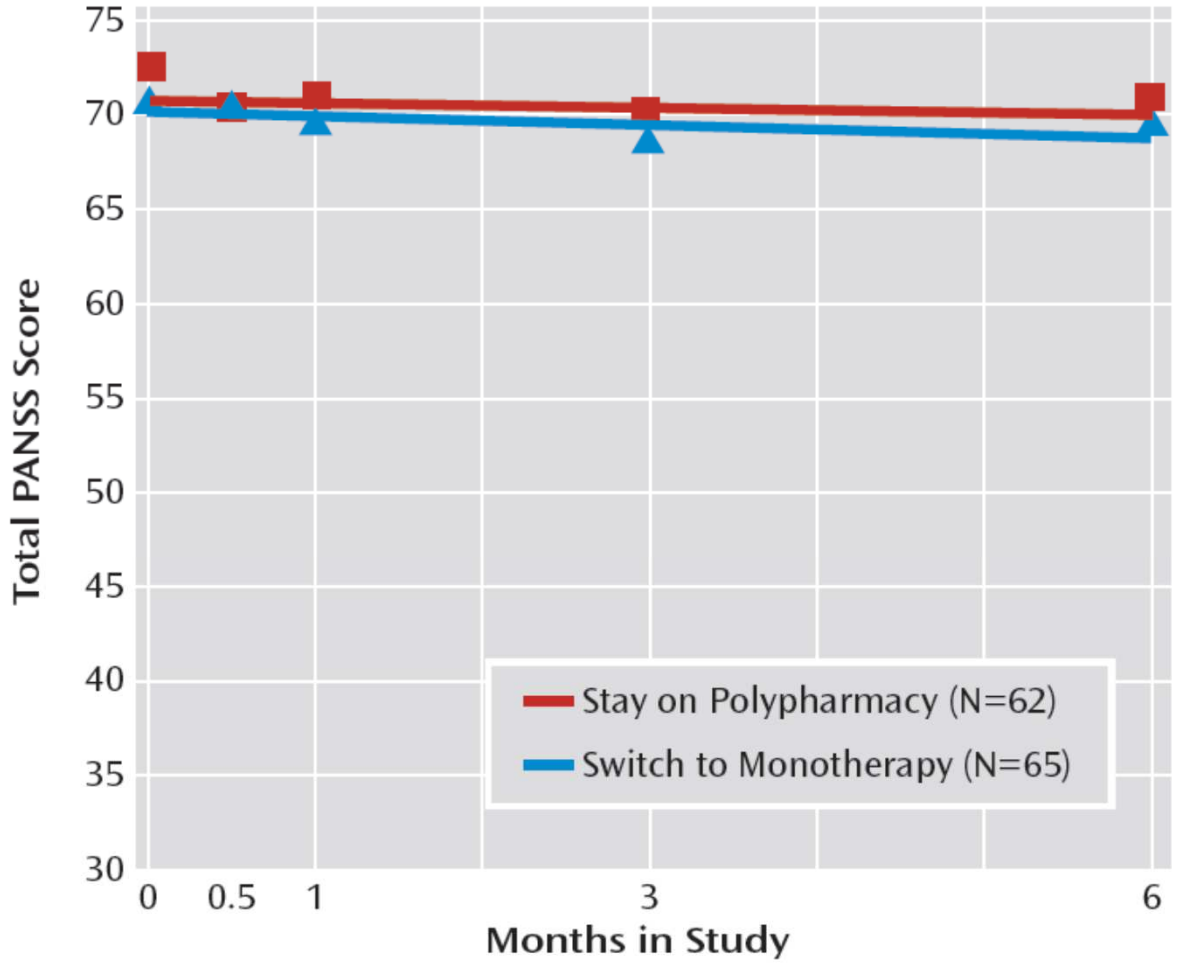
Time to Medication Change for Any Reason Among Patients Randomly Assigned Either to Stay on Antipsychotic Polypharmacy or to Switch to Monotherapy[a]

[a] Kaplan-Meier Mantel-Cox χ^2=4.55, df=1, p=0.03. In Cox regression analyses, treatment group remained significant above and beyond gender and race (Wald χ^2=4.22, df=1, p=0.04). Indicated N values refer to baseline counts.

Essock S et al. 2011: Am J Psychiatry; 168: 702-8

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Kombination: Antipsychotikum+Antipsychotikum (2)



PANSS Score Over Time Among Patients Randomly Assigned Either to Stay on Antipsychotic Polypharmacy or to Switch to Monotherapy[a]

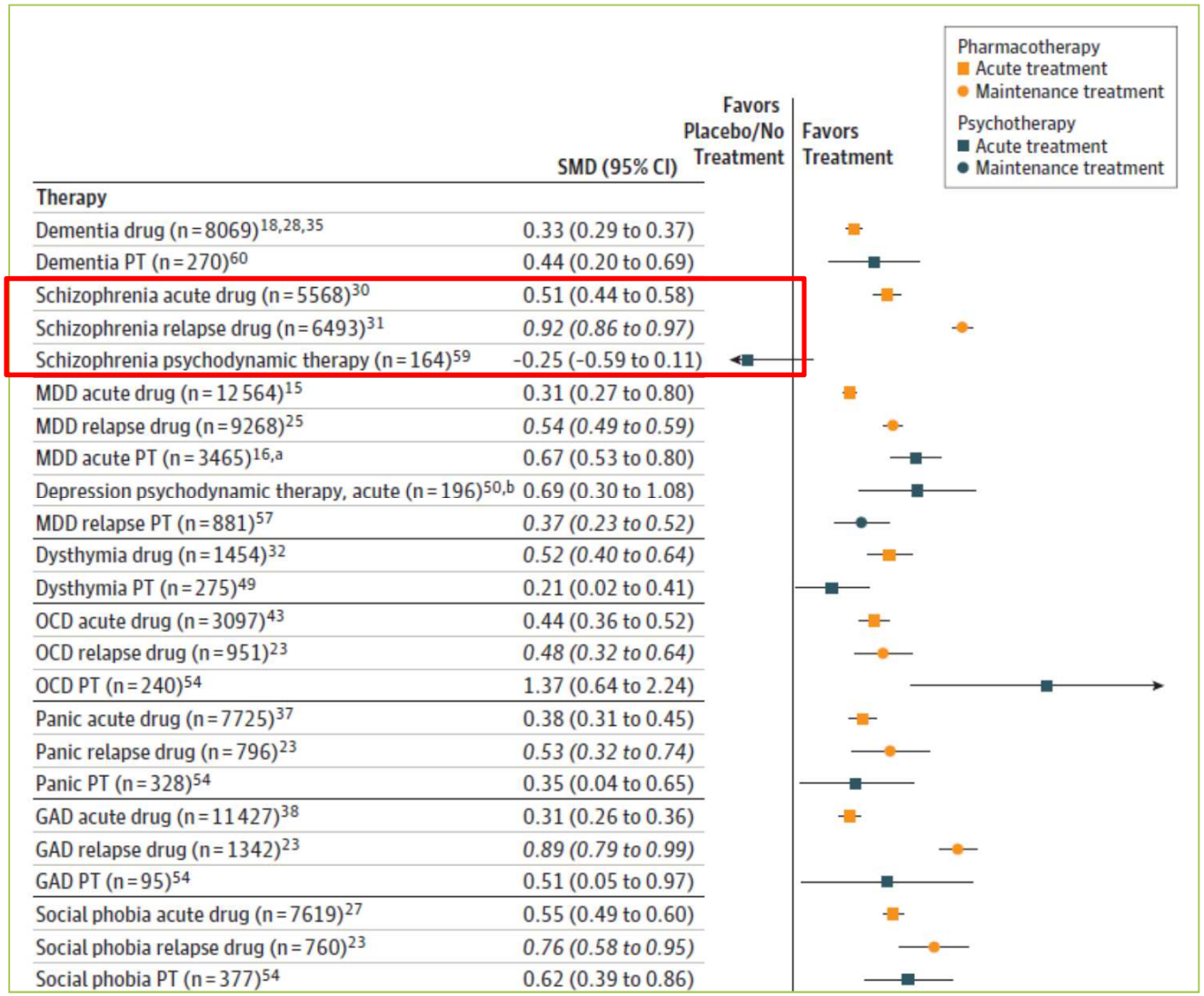
[a] No significant group-by-time interaction was observed, nor any significant effects for gender, race, or time. Indicated N values refer to baseline counts.

Essock S et al. 2011: Am J Psychiatry; 168: 702-8

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

What works?

Comparison of effect sizes in meta-analyses of acute maintenance treatment in pharmacotherapy and psychotherapy



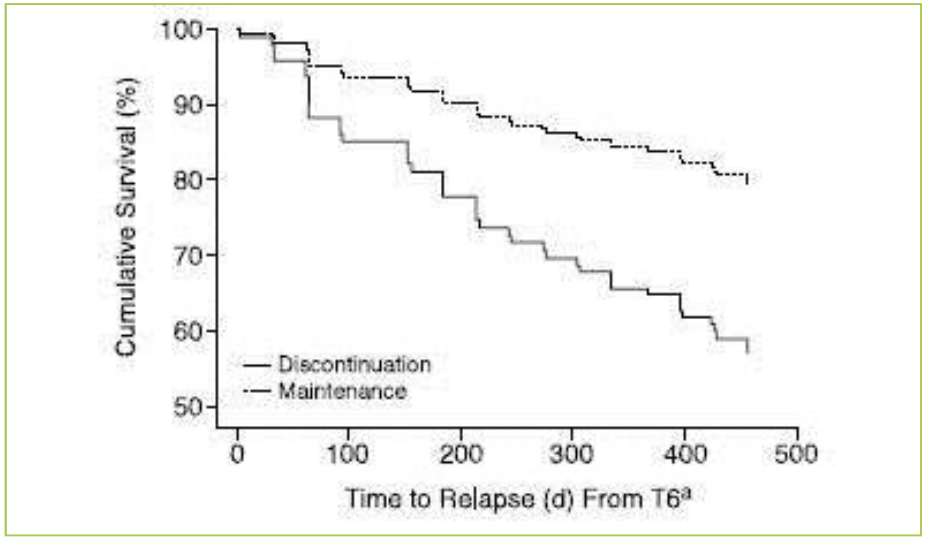
Therapy	SMD (95% CI)
Dementia drug (n = 8069)[18,28,35]	0.33 (0.29 to 0.37)
Dementia PT (n = 270)[60]	0.44 (0.20 to 0.69)
Schizophrenia acute drug (n = 5568)[30]	0.51 (0.44 to 0.58)
Schizophrenia relapse drug (n = 6493)[31]	*0.92 (0.86 to 0.97)*
Schizophrenia psychodynamic therapy (n = 164)[59]	-0.25 (-0.59 to 0.11)
MDD acute drug (n = 12 564)[15]	0.31 (0.27 to 0.80)
MDD relapse drug (n = 9268)[25]	*0.54 (0.49 to 0.59)*
MDD acute PT (n = 3465)[16,a]	0.67 (0.53 to 0.80)
Depression psychodynamic therapy, acute (n = 196)[50,b]	0.69 (0.30 to 1.08)
MDD relapse PT (n = 881)[57]	*0.37 (0.23 to 0.52)*
Dysthymia drug (n = 1454)[32]	*0.52 (0.40 to 0.64)*
Dysthymia PT (n = 275)[49]	0.21 (0.02 to 0.41)
OCD acute drug (n = 3097)[43]	0.44 (0.36 to 0.52)
OCD relapse drug (n = 951)[23]	*0.48 (0.32 to 0.64)*
OCD PT (n = 240)[54]	1.37 (0.64 to 2.24)
Panic acute drug (n = 7725)[37]	0.38 (0.31 to 0.45)
Panic relapse drug (n = 796)[23]	*0.53 (0.32 to 0.74)*
Panic PT (n = 328)[54]	0.35 (0.04 to 0.65)
GAD acute drug (n = 11 427)[38]	0.31 (0.26 to 0.36)
GAD relapse drug (n = 1342)[23]	*0.89 (0.79 to 0.99)*
GAD PT (n = 95)[54]	0.51 (0.05 to 0.97)
Social phobia acute drug (n = 7619)[27]	0.55 (0.49 to 0.60)
Social phobia relapse drug (n = 760)[23]	*0.76 (0.58 to 0.95)*
Social phobia PT (n = 377)[54]	0.62 (0.39 to 0.86)

Huhn M et al. 2014: JAMA Psychiatry; 71(6): 706-15

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

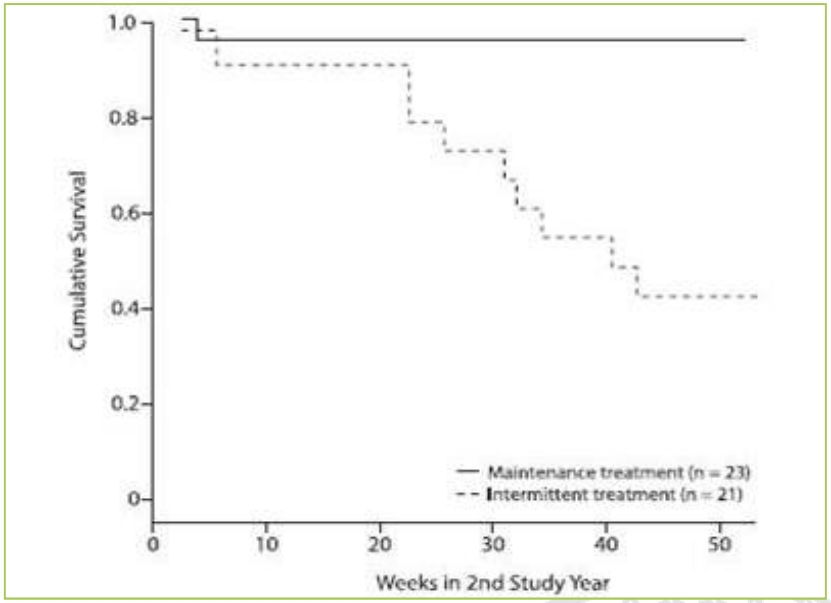
Behandlungsdauer: kontinuierlich vs. intermittierend

Relapse rates for discontiuation stategies versus maintenance treatment (survival function)



Wunderink L et al. 2007: J Clin Psychiatry 68(5):654-61

Survival Analysis for clinical deterioration for patients recieving maintenance antipsychotic versus intermittent treatment



Gaebel W et al. 2010: J Clin Psychiatry 72(2):205-18

- **Preferable continuous treatment !**
- **No intermittent treatment !**

Hasan A et al. 2012: World J Biol Psychiatry; 13: 318-78

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Qualitätssicherung über Messung der Nebenwirkungen

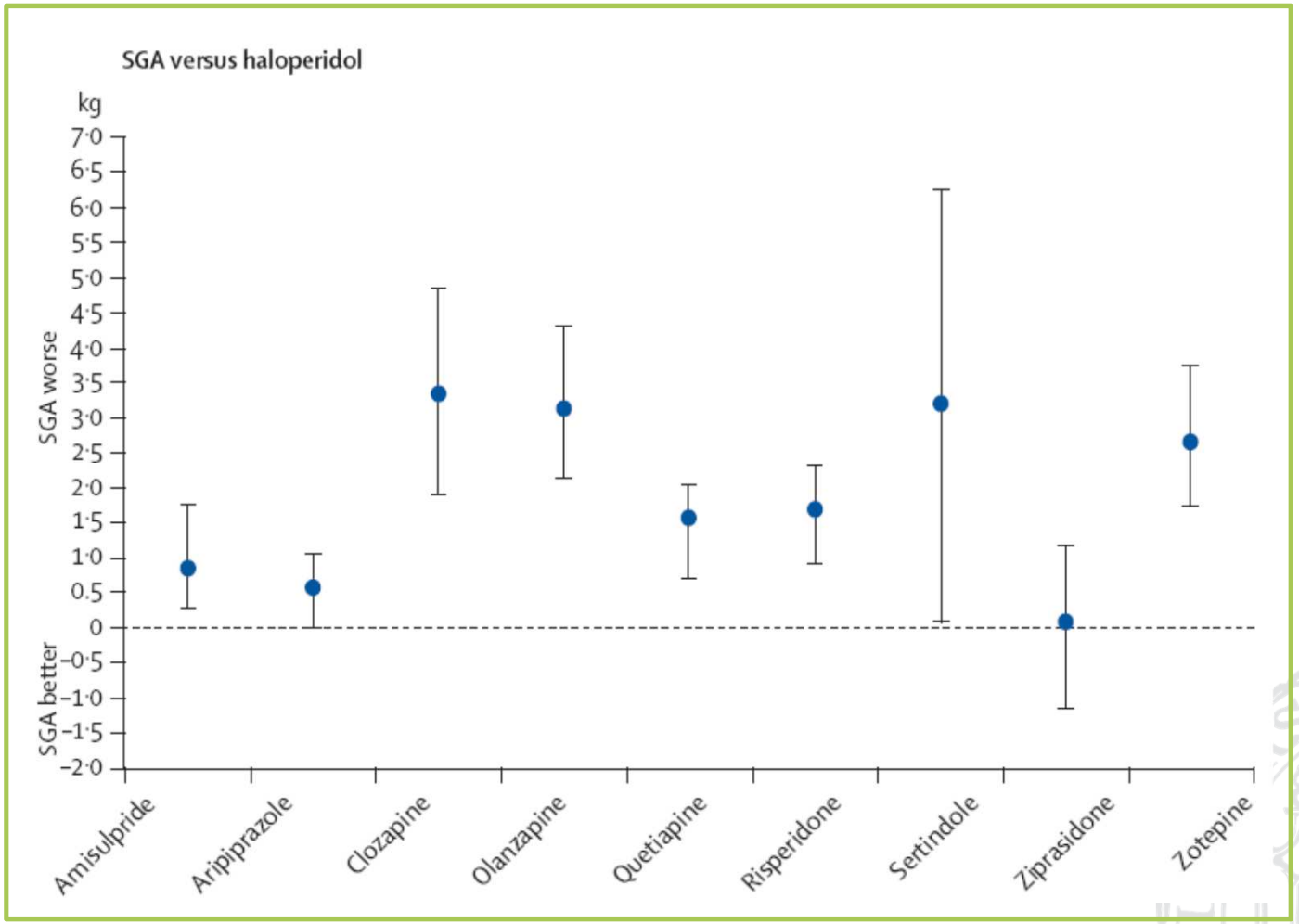
Nebenwirkungen (1): Erhöhtes Risiko für motorische Nebenwirkungen

- Acute dystonia
- Parkinsonoid
- Akathisia
- Tardive dyskinesia
- Malignant neuroleptic syndrome (MNS)

Hasan A et al. 2012: World J Biol Psychiatry; 13: 318-78

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Nebenwirkungen (2): Gewichtszunahme in kg



Leucht et al. 2009: Lancet 3;373(9657):31-41

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

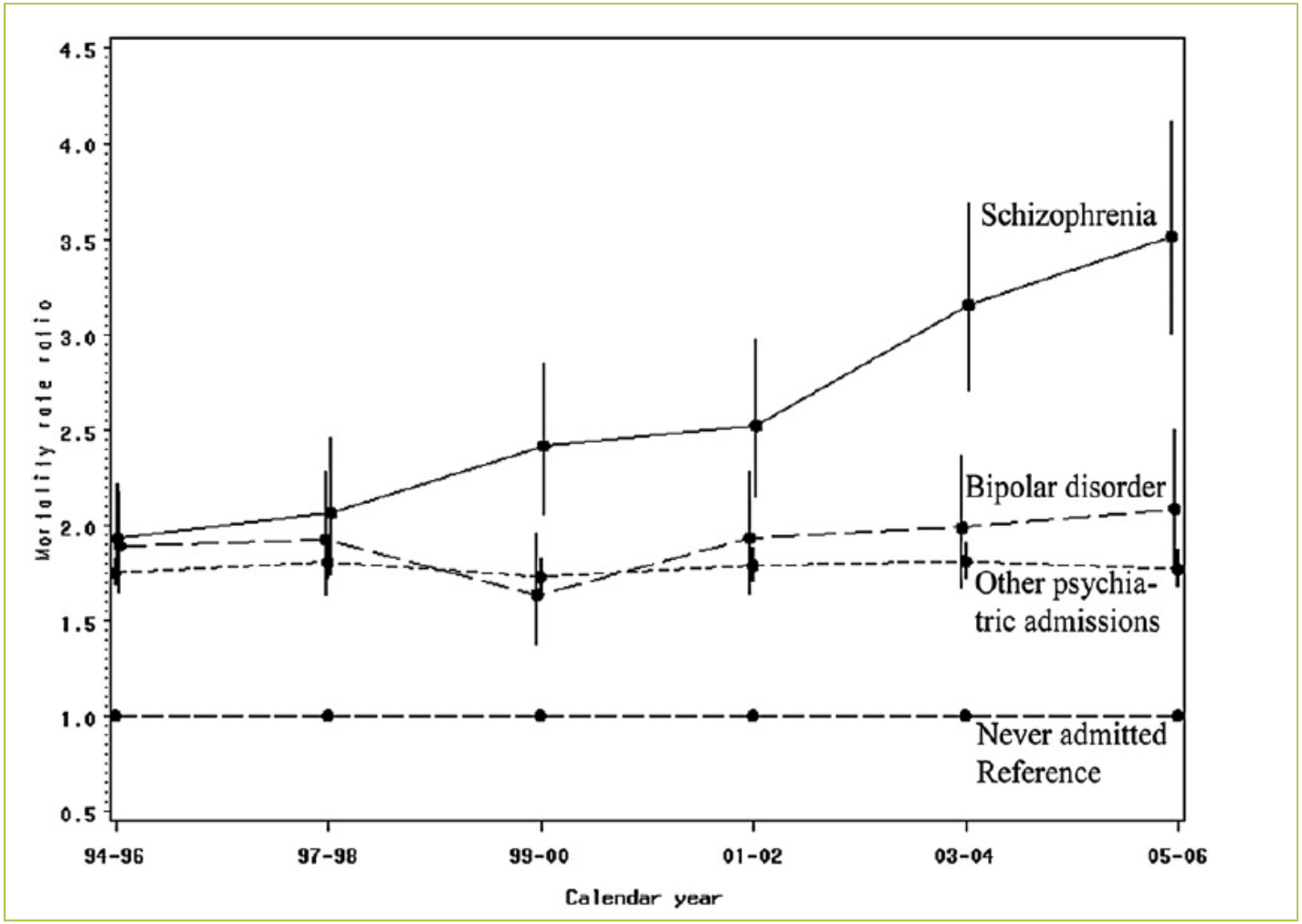
Nebenwirkungen (3): Interventionsmöglichkeiten beim metabolischen Syndrom

Intervention/Drug	Category of evidence[a]	Recommendation[b]
Psychosocial intervention	C	4[1]
Switch to aripiprazole	A	2[2]
Switch to ziprasidone	B	3[2]
Amantadine	C	4
H2-receptor antagonists	C	4
Metformin	D	5
Modafinil	F	—
Orlistat	F	—
Rosaglitazone	F	—
Rosaglitazone + clozapine	C	4
Sibutramine	F	—
Sibutramine + olanzapine	C	4
Topiramate	C	4
Topiramate + olanzapine	B	3

Hasan A et al. 2013: World J Biol Psychiatry; 14:2-44

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Nebenwirkungen (4): Erhöhtes Risiko für kardiovaskuläre Erkrankungen

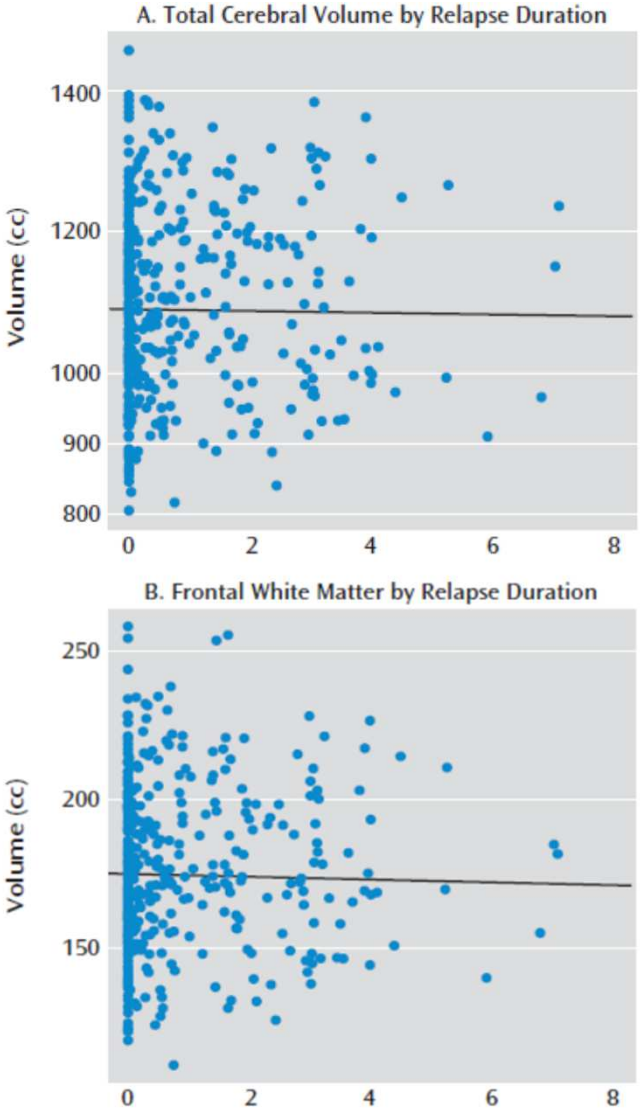


Mortality rate ratio (MRR) of heart disease mortality among persons with schizophrenia, bipolar disorder, and other psychiatric disorders, compared with persons with no psychiatric admissions (reference group).
Men and women combined

Laursen TM and Nordentoft M 2011: Journal of Psychiatric Research;45:29e35

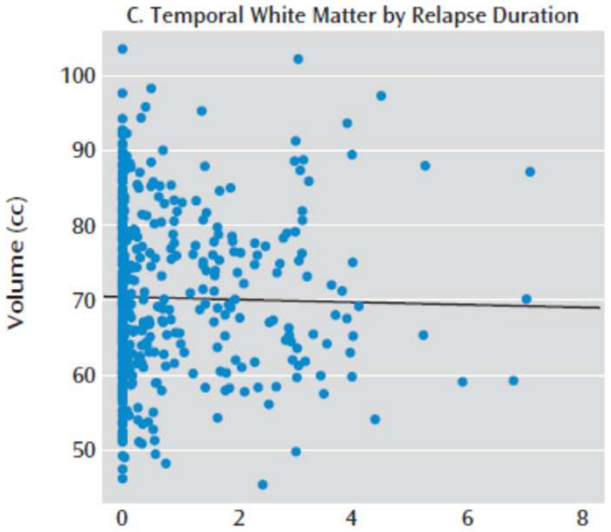
http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Nebenwirkungen (5): Antipsychotika und hirnstrukturelle Veränderungen



Relapse Duration (years)

Relationships Between Brain Volumes and Relapse Duration in a Longitudinal Study of 202 Schizophrenia Patients[a]



[a] Longer duration of symptomatic relapse was significantly associated with smaller total cerebral brain tissue volume (panel A; β_2=–1.55 cc/year), frontal lobe white matter volume (panel B; β_2=–0.48 cc/year), and temporal lobe white matter volume (panel C; β_2=–0.17 cc/year). Linear regression lines with negative slopes were generated based on longitudinal brain volume measures.

Andreasen N et al. 2013: Am J Psychiatry; 170: 609-15

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Messung der Verhaltensänderung jenseits der Psychopathologie

Veränderungen (1):Neuropsychologie

Digit Span (short-term test memory)
VLMT (Verbal Learning and Memory Test)
Regensburger Wortflüssigkeitstest (Regensburg Word Fluency Test (RWT))
TMT A and B (Trail Making Test)
WCST (Wisconsin Card Sorting Test)

Veränderungen (2): Funktion

- **GAF (**Global Assessment of Functioning) **improves significantly in 10 points from 56 to 66 ➔ One step up in the exercise level to the next stage**
- **SZ-Sports baseline (56) lower than SZ-Controls (62,6)**

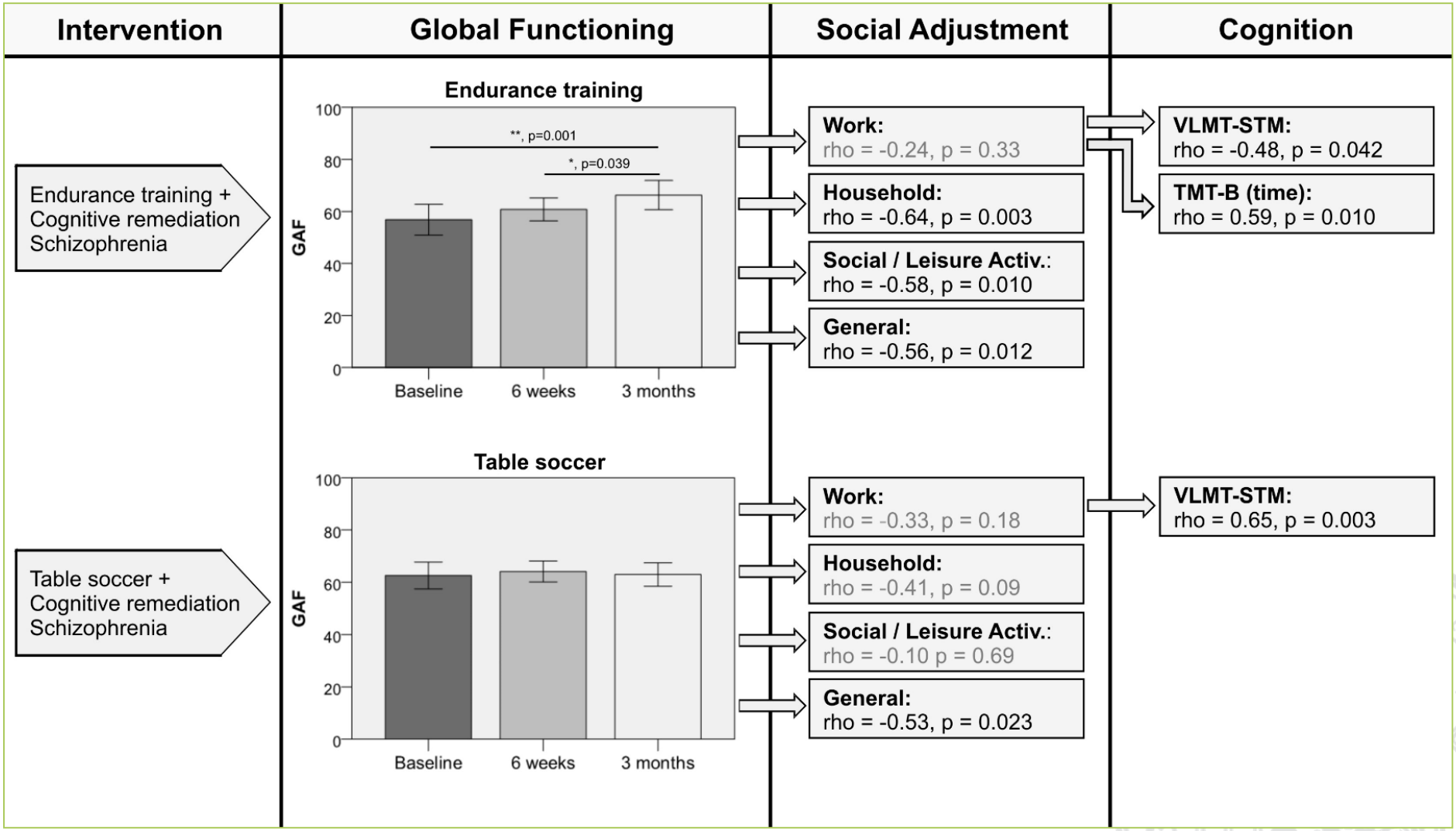
Disturbing symptoms GAF 56	Improvement GAF 66
Moderate symptoms (e.g. affective flattening, elaborate speech, occasional panic attacks)	Few mild symptoms (e.g. depressive mood)
	Mild sleeplessness
moderate difficulties in coping with social environment, work or school (e.g. few friends, conflicts with colleagues, class mates or difficulties in maintaining/dealing with interpersonal relationships)	Few mild difficulties in coping with social environment, work or school (e.g. occasional skipping school or petty theft in household, but generally good capability and or ability to maintain interpersonal relationships)

Less Symptoms (negative) ➔ better adaptation to work and social contacts

Malchow B et al. 2015: Schiz Bull; in revision

http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html

Veränderungen (3): Funktionsverbesserungen durch Ergometer-Training (3 Monate) und Cogpack (+6 Wochen)



Malchow B et al. 2015: Schiz Bull; in revision

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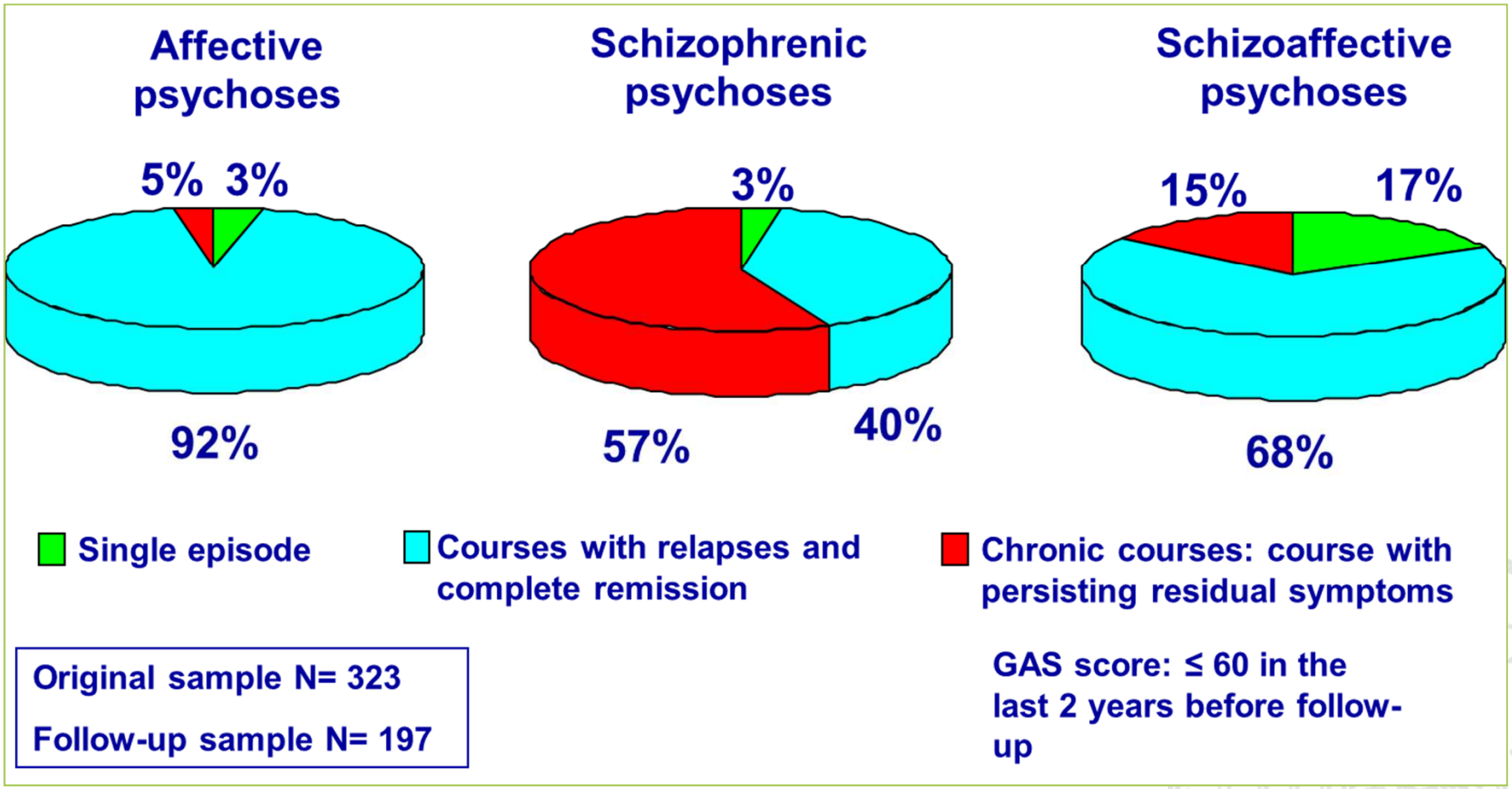
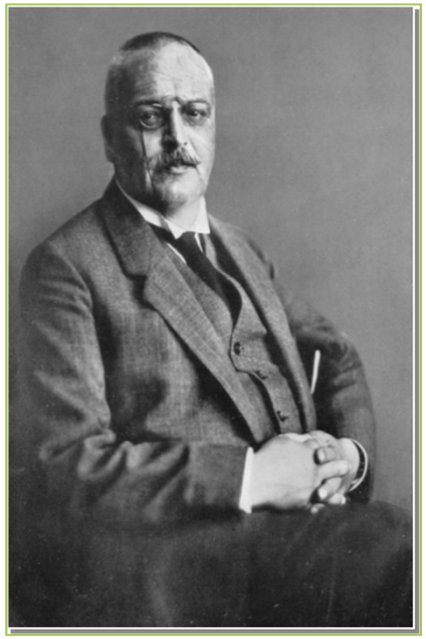
Veränderungen (3): Remissionsgrad



Möller HJ 2011: Eur Psychiatry: 26(4):231-43

Zusammenfassung

- **Qualitätssicherung muß in der Pharmakotherapie erfolgen, da sie eine der wirkungsvollsten, aber auch am meisten kritisiertesten Therapiepfeiler darstellt**
- **Eine gute Option zur Qualitätssicherung ist die Orientierung an Leitlinien**
- **Die Qualität der Pharmakotherapie kann an der Wirkung der Psychopharmaka (hier: Antipsychotika) gemessen werden: Auswahl; Dosierung; Behandlungsdauer bis zur Umstellung; Kombinationstherapie; Behandlungsdauer insgesamt**
- **Die Qualität der Pharmakotherapie kann an den Nebenwirkungen der Psychopharmaka (hier: Antipsychotika) gemessen werden: Motorik; Metabolik; Zerebral**
- **Die Verhaltensänderung unter Pharmakotherapie kann neben der der Psychopathologie, der Neuropsychologie auch anhand der Funktionsverbesserung gemessen werden.**



Vielen Dank für Ihre Aufmerksamkeit