Todesursache Schizophrenie?

Klinik für Psychiatrie und Psychotherapie
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J. Gallinat

Lebenserwartung

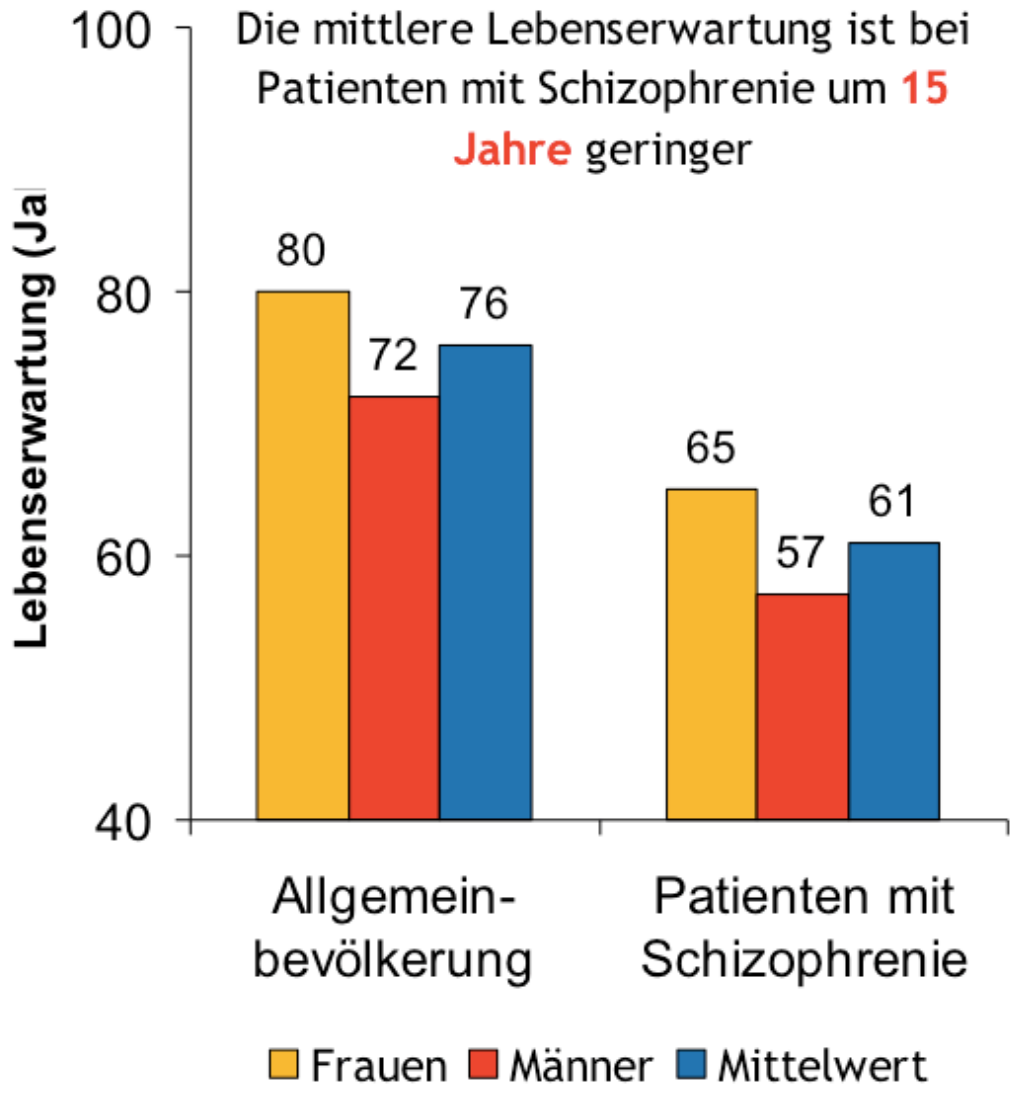


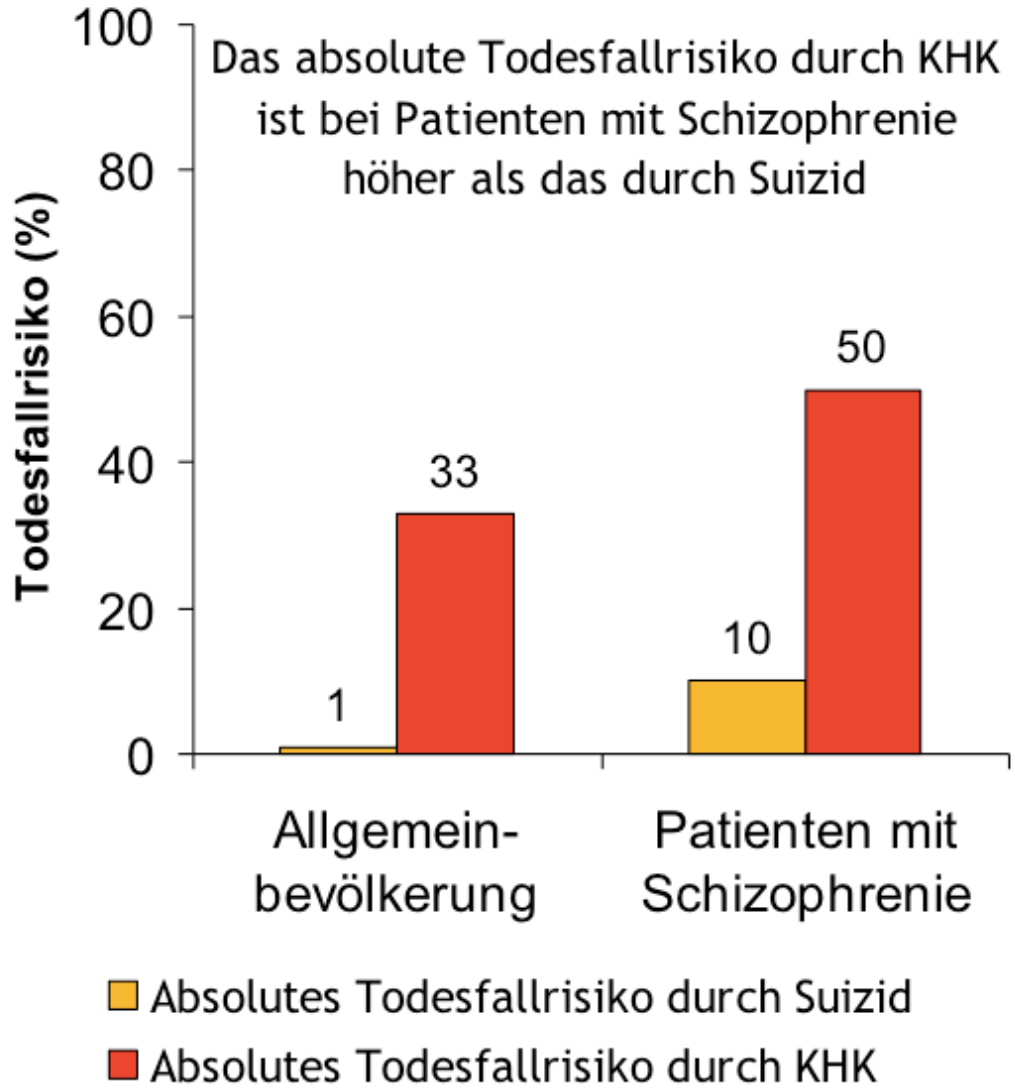
Table 1. SMRs for Schizophrenia by Cause of Death for All Persons

Causes of Death	No. of SMRs	Quantile					Mean (SD)	Geometric Mean
		10%	25%	Median	75%	90%		
All-Cause and Middle-Level Categories								
All-cause (*ICD-9* codes 001-799/E800-E999)	38	1.18	1.87	2.58	3.64	5.76	2.98 (1.75)	2.68
All-natural cause (*ICD-9* codes 001-799)	6	0.99	1.04	2.41	2.90	4.10	2.31 (1.18)	2.03
All-unnatural cause (*ICD-9* codes E800-E999)	3	5.56	5.56	7.50	12.73	12.73	8.60 (3.71)	8.10
Natural Causes, Cause Specific								
Cardiovascular diseases (*ICD-9* codes 390-429)	7	1.11	1.40	1.79	2.49	3.60	2.01 (0.83)	1.88
Cerebrovascular diseases (*ICD-9* codes 430-438)	3	0.61	0.61	0.69	1.30	1.30	0.87 (0.38)	0.82
Digestive diseases (*ICD-9* codes 520-579)	5	1.79	2.24	2.38	2.50	17.50	5.28 (6.84)	3.34
Endocrine diseases (*ICD-9* codes 250-259)	3	2.20	2.20	2.63	11.66	11.66	5.50 (5.34)	4.07
Infectious diseases (*ICD-9* codes 001-139)	3	1.60	1.60	4.29	7.80	7.80	4.56 (3.11)	3.77
Genitourinary diseases (*ICD-9* codes 580-629)	3	1.54	1.54	3.70	4.29	4.29	3.18 (1.45)	2.90
Neoplastic diseases (*ICD-9* codes 140-239)	7	0.71	1.00	1.37	2.01	2.40	1.44 (0.60)	1.33
Nervous diseases (*ICD-9* codes 345-349)	4	1.60	1.95	4.22	6.57	7.00	4.26 (2.70)	3.55
Respiratory diseases (*ICD-9* codes 460-519)	6	2.20	2.39	3.19	3.80	9.30	4.01 (2.66)	3.51
Other diseases (*ICD-9* codes 1-389/630-799)	3	1.45	1.45	2.00	3.40	3.40	2.28 (1.01)	2.14
Unnatural Causes, Cause Specific								
Accident (*ICD-9* codes E800-E949)	6	1.20	1.63	1.73	5.10	8.40	3.30 (2.88)	2.51
Suicide (*ICD-9* codes E950-E959)	10	0.66	5.90	12.86	21.43	174.25	43.47 (95.11)	16.13

Männer und Frauen gleich betroffen
SMR steigt über die letzten 3 Dekaden an (p=0.03)
Probleme:
- **welchen Effekt hat die Medikation,**
- **tatsächliche Todesursachen**

Saha et al. 2007, Arch Gen Psychiatry

Lebenserwartung



Schizophrenie-
Mortalität und Komorbidität

- Vor der Ära der Neuroleptika war die Mortalität schizophrener Patienten gegenüber der Allgemeinbevölkerung erhöht
  - 1925-1929 fünfach (Walz; Dissertation 1991 Zürich; n=3.700)
  - 1924-1936 drei- bis fünffach (Skandinavische Studien; n=>30.000)
  - Nach 1957 ca. 1,5 bis dreifach (12 Studien in der Neuroleptikaära)
- In der Ära der Neuroleptika
  - Mortalität unter Placebo höher als unter Typika und Atypika (Khan et al. 2007; FDA-Datenbank Analyse 1982-2002)
  - Suizidrate seit Einführung der NL unverändert aber nach Atypika reduziert (Baldessarini et al. 2003)

Plötzlicher Herztod

Verlängertes QTc- Intervall

↓

Polymorphe Kammertachyarrhythmie,
Typ „Torsades de Pointes“ („Umkehr der Spitzen“)**,**
potenziell lebensbedrohlich

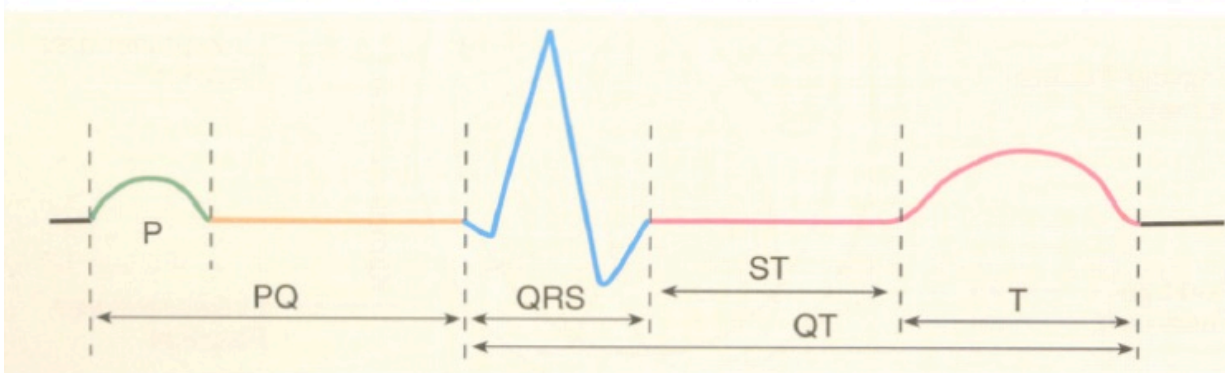
↓

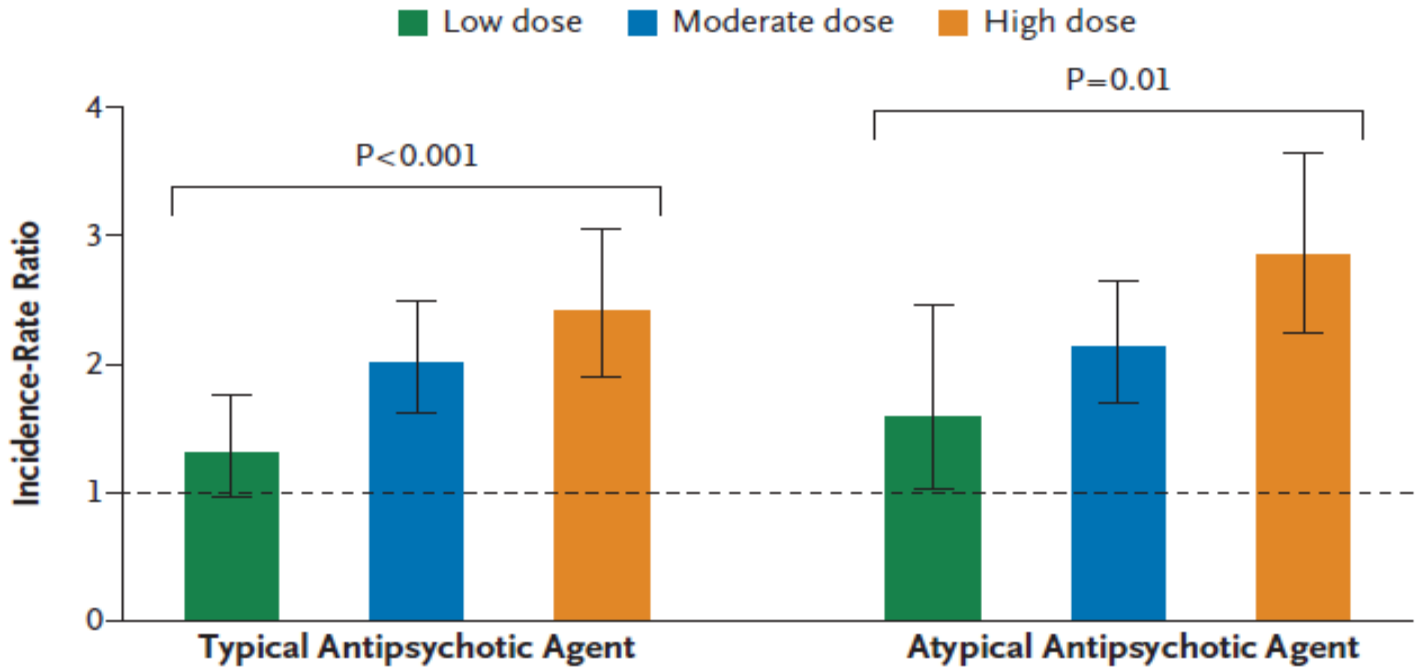
Plötzlicher Herztod (Sekundentod),
sudden death

Grenzwert
ca. 440 ms

mittlerweile Männer=Frauen
bei >500ms absetzen!

Schwindel, Palpi-
tationen, Synkopen



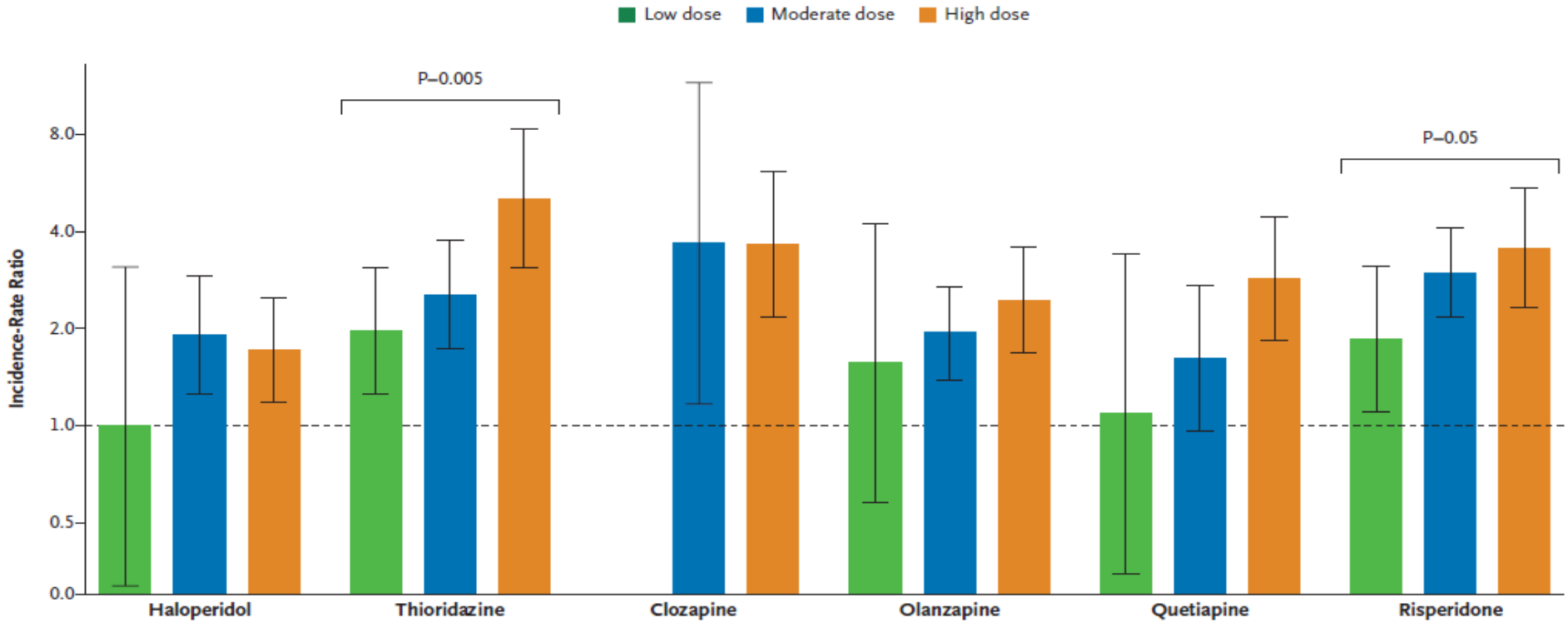


No. of Deaths	46	104	105	22	108	93
No. of Person-Years	21,438	33,671	31,626	10,435	41,513	27,641
Incidence-Rate Ratio	1.31	2.01	2.42	1.59	2.13	2.86
95% CI	0.97–1.77	1.62–2.50	1.91–3.06	1.03–2.46	1.70–2.65	2.25–3.65

Figure 1. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death among Current Users of Antipsychotic Drugs, According to Type of Drug and Dose.

Doses are shown as chlorpromazine equivalents: low dose, <100 mg; moderate dose, 100 to 299 mg; high dose, 300 mg or more. The reference category is nonusers of antipsychotic drugs. P values are for a dose–response relationship. I bars indicate 95% confidence intervals.

Ray et al. 2009, NEJM



No. of Deaths	3	23	32	20	28	17	0	3	16	4	40	31	3	15	22	15	46	24
No. of Person-Years	1342	7014	13,372	6238	7254	2223	63	593	3999	1640	15,395	10,222	2433	7983	6939	5894	12,950	5745
Incidence-Rate Ratio	1.00	1.92	1.72	1.97	2.55	5.05	—	3.67	3.66	1.57	1.94	2.45	1.09	1.62	2.85	1.86	2.98	3.56
95% CI	0.3–3.1	1.3–2.9	1.2–2.5	1.3–3.1	1.7–3.8	3.1–8.3	—	1.2–11.5	2.2–6.1	0.6–4.2	1.4–2.7	1.7–3.6	0.3–3.4	1.0–2.7	1.8–4.4	1.1–3.1	2.2–4.1	2.3–5.4

Figure 2. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death among Current Users of Six Frequently Prescribed Antipsychotic Drugs, According to Dose.

Doses are shown as chlorpromazine equivalents: low dose, <100 mg; moderate dose, 100 to 299 mg; high dose, 300 mg or more. The reference category is nonusers of any antipsychotic drug. P values are for a dose–response relationship. I bars indicate 95% confidence intervals.

Ray et al. 2009, NEJM

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ORIGINAL REPORT

Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database

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Aim To describe spontaneously reported cases of torsades de pointes (TdP) in Sweden and to investigate if this adverse drug reaction (ADR) was labelled in the summary of product characteristics (SPC) for the drugs implicated.
Methods Reported cases of TdP 1991–2006 were identified and evaluated with regard to drug use and other possible risk factor.

Table 1. Drugs (total $n = 116$) implicated as suspected QT prolonging agents in 88 cases of TdP reported to the swedish pharmacovigilance database (SWEDIS) between January 1991 and February 2006

Suspected drugs	Total number; $n = 116$ (Number as single suspected agent; $n = 64$)	TdP or QT-prolongation in the SPC	TdP or QT-prolongation in articles/website	References (w = www.torsades.org (list 1))
Cardiac drugs				
Sotalol	58(46)	Yes	Yes	1, 2, 4, 6, 7, 11, w
Digoxin	10(0)			
Disopyramide	5(4)	Yes	Yes	1, 2, 4, 6, 7, 11, w
Quinidine	2(1)	Yes	Yes	1, 2, 4, 6, 7, 11, w
Metoprolol	4(0)			
Adenosine	1(0)		Yes	6
Amiodarone	1(1)		Yes	1, 2, 4, 6, 7, 11, w
Flecainide	1(0)		Yes	6
Ibutilide	1(1)	Yes	Yes	1, 2, 4, 6, 11, w
Levosimendan	1(1)			
Prenalterol	1(0)	NA		
Antidepressants				
Citalopram	9(5)			
Fluoxetine	2(1)		Yes	11
Amitriptyline	1(1)	Yes	Yes	1, 2, 4, 6, 7, 9, 10, 11
Clomipramine	1(0)	Yes		
Moclobemide	1(1)			
Nortriptyline	1(0)			
Paroxetine	1(0)			
Antipsychotics				
Alimemazine	1(0)			
Chlorpromazine	1(0)	Yes		
Clomethiazole	1(0)			
Haloperidol	1(0)	Yes		
Antibiotics				
Erythromycin	2 (2)	Yes		
Others				
Cisapride	3(0)	NA		
Etanercept	1(0)			
Loratadine	1(0)			
Ginseng	1(0)			
Terfenadine	1(0)	NA		
Thiethylperazine	1(0)			
Timolol (eye drops)	1(0)			

SPC, summary of product characteristics.

NA, not applicable.

KEY POINTS

- Cardiac drugs are most often suspected in TdP/QT prolongation reports.
- Citalopram was implicated in several reports but this suspected adverse drug reaction is not listed in its SPC.
- Most patients had more than one risk factor in addition to medication.
- TdP/QT prolongation were not labelled in the SPC for two third of the drugs recorded in the reports.

Mortalität unter Neuroleptika

11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study)

Jari Tiihonen, Jouko Lönnqvist, Kristian Wahlbeck, Timo Klaukka, Leo Niskanen, Antti Tanskanen, Jari Haukka

Summary

Background The introduction of second-generation antipsychotic drugs during the 1990s is widely believed to have adversely affected mortality of patients with schizophrenia. Our aim was to establish the long-term contribution of antipsychotic drugs to mortality in such patients.

Methods Nationwide registers in Finland were used to compare the cause-specific mortality in 66 881 patients versus the total population (5·2 million) between 1996, and 2006, and to link these data with the use of antipsychotic drugs. We measured the all-cause mortality of patients with schizophrenia in outpatient care during current and cumulative exposure to any antipsychotic drug versus no use of these drugs, and exposure to the six most frequently used antipsychotic drugs compared with perphenazine use.

Findings Although the proportional use of second-generation antipsychotic drugs rose from 13% to 64% during follow-up, the gap in life expectancy between patients with schizophrenia and the general population did not widen between 1996 (25 years), and 2006 (22·5 years). Compared with current use of perphenazine, the highest risk for overall mortality was recorded for quetiapine (adjusted hazard ratio [HR] 1·41, 95% CI 1·09–1·82), and the lowest risk for clozapine (0·74, 0·60–0·91; p=0·0045 for the difference between clozapine *vs* perphenazine, and p<0·0001 for all other antipsychotic drugs). Long-term cumulative exposure (7–11 years) to any antipsychotic treatment was associated with lower mortality than was no drug use (0·81, 0·77–0·84). In patients with one or more filled prescription for an antipsychotic drug, an inverse relation between mortality and duration of cumulative use was noted (HR for trend per exposure year 0·991; 0·985–0·997).

Interpretation Long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use. Second-generation drugs are a highly heterogeneous group, and clozapine seems to be associated with a substantially lower mortality than any other antipsychotics. Restrictions on the use of clozapine should be reassessed.

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Mortalität unter Neuroleptika

- Einschluss aller Pat. Finnlands mit Schizophrenie und SAP 1973-2004
- Beginn der Verlaufsuntersuchung 1996 (da erst ab hier Daten zur Verschreibungspraxis verfügbar) bis 2007 (11 Jahre)
  - 18.914 (ambulant) unmedizierte Patienten (0,4 Jahre stationär)
  - 47.967 (ambulant) medizierte Patienten (0,3 Jahre stationär)

- Verlinkung von
  - National Hospital Discharge Register (alle stationär Behandelten)
  - Statistics Finland (Aufzeichnung aller Todesfälle und -ursachen)
  - Social Insurance Institution of Finland (Erfassung aller erstatteten Rezepte; Ausgabedatum und Dosis)

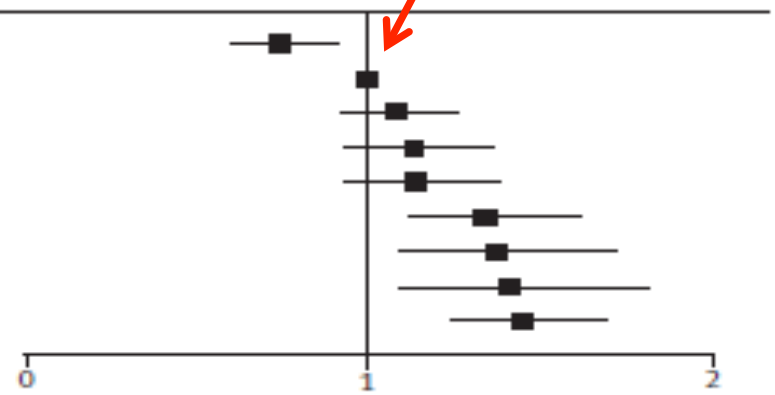
Mortalität unter Neuroleptika

Gesamttodesfallrisiko:
Periode *mit* NL vs. Periode *ohne* NL (alle) HR 0,68

adjustiert auf Todesfälle unter Perphenazin

Risiko alle Todesursachen (Monotherapie)

A	Number of deaths	Person-years	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
Clozapine	182	32 000	5·69	0·53 (0·43–0·65)	0·74 (0·60–0·91)
Perphenazine	193	17 930	10·77	1·00	1·00
Polypharmacy	1481	132 320	11·19	1·04 (0·89–1·21)	1·08 (0·92–1·26)
Olanzapine	264	25 130	10·50	0·98 (0·81–1·17)	1·13 (0·93–1·36)
Thioridazine	227	18 420	12·32	1·14 (0·94–1·39)	1·14 (0·93–1·38)
Risperidone	295	19 410	15·20	1·41 (1·18–1·69)	1·34 (1·12–1·62)
Haloperidol	135	7040	19·19	1·78 (1·43–2·22)	1·37 (1·10–1·72)
Quetiapine	89	5360	16·60	1·54 (1·20–1·98)	1·41 (1·09–1·82)
Other	1234	70 520	17·50	1·63 (1·40–1·89)	1·45 (1·24–1·69)



Tiihonen et al. 2013

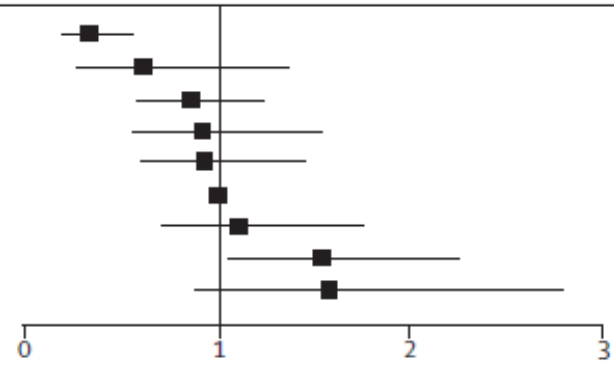
Mortalität unter Neuroleptika

Gesamttodesfallrisiko:

Periode *mit* NL vs. Periode *ohne* NL (alle) HR 0,68

Suizid

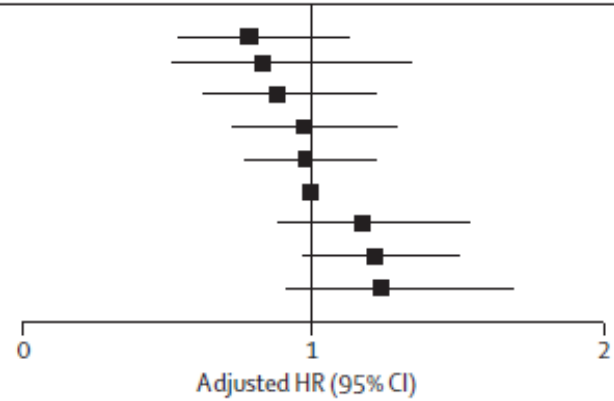
	Number of deaths	Person-years	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
Clozapine	27	32000	0·84	0·46 (0·28–0·76)	0·34 (0·20–0·57)
Haloperidol	7	7040	1·00	0·54 (0·24–1·22)	0·61 (0·27–1·37)
Polypharmacy	226	132320	1·71	0·93 (0·64–1·34)	0·86 (0·59–1·24)
Thioridazine	27	18420	1·47	0·80 (0·48–1·32)	0·93 (0·56–1·55)
Olanzapine	57	25130	2·27	1·23 (0·80–1·89)	0·94 (0·61–1·45)
Perphenazine	33	17930	1·84	1·00	1·00
Risperidone	47	19410	2·42	1·32 (0·84–2·05)	1·12 (0·72–1·76)
Other	194	70520	2·75	1·49 (1·03–2·16)	1·55 (1·07–2·25)
Quetiapine	19	5360	3·54	1·93 (1·09–3·39)	1·58 (0·89–2·79)



Herzinfarkt

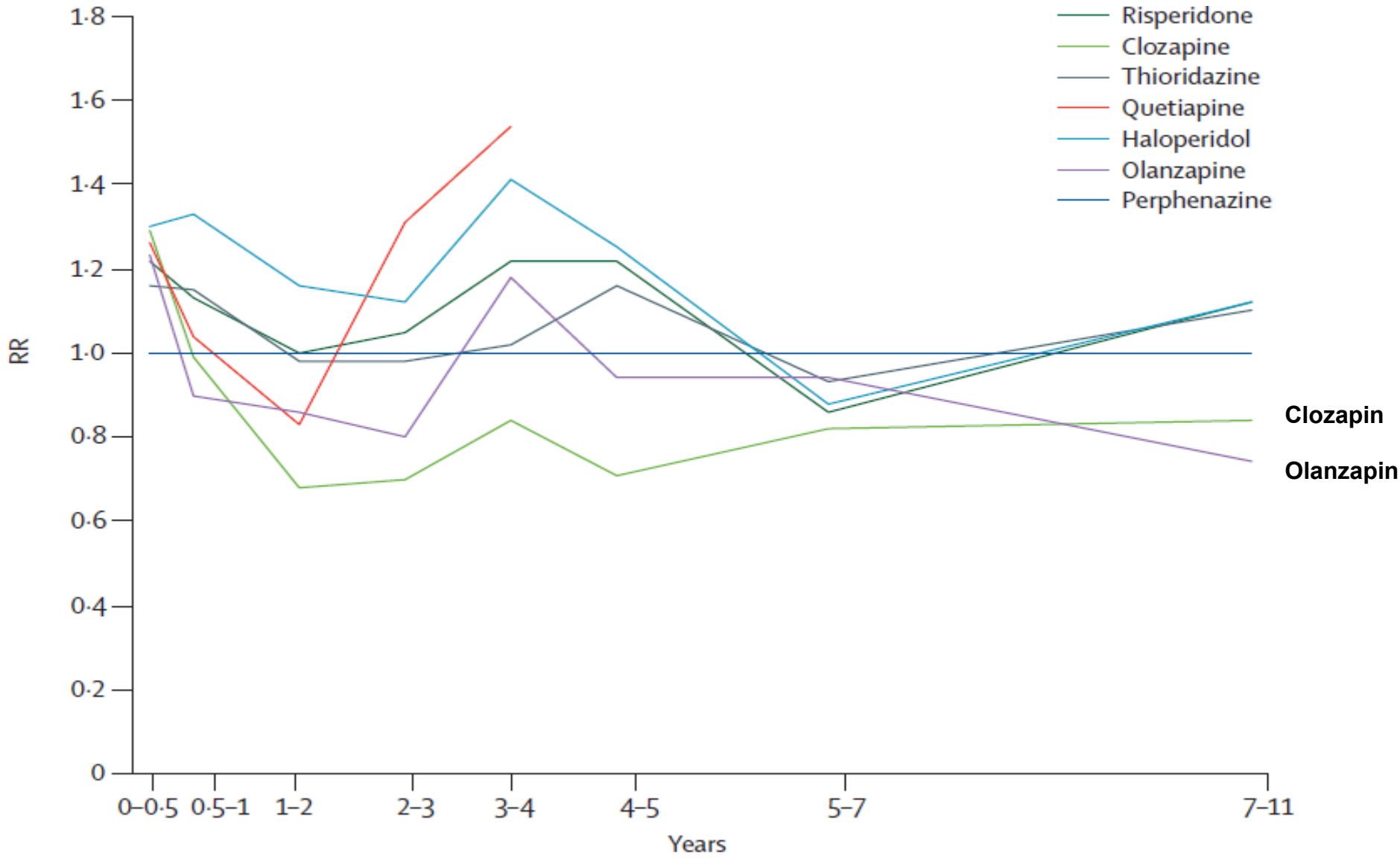
C

Clozapine	42	32000	1·31	0·25 (0·17–0·35)	0·78 (0·54–1·12)
Quetiapine	21	5360	3·92	0·73 (0·46–1·17)	0·83 (0·52–1·34)
Olanzapine	65	25130	2·59	0·48 (0·35–0·66)	0·88 (0·63–1·21)
Thioridazine	104	18420	5·65	1·05 (0·80–1·39)	0·97 (0·73–1·29)
Polypharmacy	522	132320	3·94	0·74 (0·59–0·92)	0·97 (0·77–1·21)
Perphenazine	96	17930	5·35	1·00	1·00
Risperidone	119	19410	6·13	1·15 (0·88–1·50)	1·17 (0·89–1·54)
Other	520	70520	7·37	1·38 (1·11–1·71)	1·21 (0·97–1·51)
Haloperidol	72	7040	10·23	1·91 (1·41–2·59)	1·24 (0·91–1·69)



Monotherapie; adjustiert auf Todesfälle unter Perphenazin

Relatives Todesrisiko im Verlauf



Clozapin

Olanzapin

- Todesfallrisiko: Lanzeitbehandlung mit NL besser als Nichtbehandlung NL
- Geringes Todesfallrisiko unter Clozapin
  - Intensiveres Monitoring ? eher nein laut Meltzer et al. 2003
  - Gute Adhärenz (Tiihonen et al. 2006) → gesunder Lebensstil ?
  - Möglicherweise 11 Jahre Verlaufsbeobachtung zu kurz für kardiovaskuläre Todesfälle

Kritik

- Keine Daten zu: Gesundheitsverhalten, Gesundheitszustand, Lebensqualität, Verheiratet, Ükonomische und Lebensstilfaktoren, Substanzmißbrauch, Rauchen, Psychotherapie, …
- Kurzer Beobachtungszeitraum; unterschiedlicher Rekrutierungszeiträume (Problem für Medikamentenanamnese)
- Gruppen unterscheiden sich in Alter und anderen Variablen
- Tod im Krankenhaus ausgenommen (allerdings nur bei akuten, nicht bei kumulativem Effekt)

Clozapin und Suizidalität

- Untersuchung der Todesursache bei 67.072 Personen (10-54 J.; 85.399 Personenjahre) die aktuell oder früher Clozapin einnahmen (national registry of clozapine recipients to the National Death Index u.a.; Berechnung der Sterberaten kontrolliert für Alter, Geschlecht und Ethnizität 1991-1993)
- 396 Todesfälle; Mortalität unter Clozapin
  - Niedriger für Suizide RR(rate ratio)=0,17; 95% CI=0,10-0.30
  - Höher für untypische Todesursachen (Lungenembolie RR=5,2 und Atemwegserkrankungen RR=2,9)
  - Insgesamt erniedrigte Mortalität (6-fach)

Walker et al. 1997

Relative Risk of Cardiovascular and Cancer Mortality in People With Severe Mental Illness From the United Kingdom's General Practice Research Database

David P. J. Osborn, PhD; Gus Levy, MSc; Irwin Nazareth, PhD; Irene Petersen, PhD; Amir Islam, MBA; Michael B. King, PhD

Context: People with severe mental illness (SMI) appear to have an elevated risk of death from cardiovascular disease, but results regarding cancer mortality are conflicting.

Objective: To estimate this excess mortality and the contribution of antipsychotic medication, smoking, and social deprivation.

Design: Retrospective cohort study.

Setting: United Kingdom's General Practice Research Database.

Patients: Two cohorts were compared: people with SMI diagnoses and people without such diagnoses.

Main Outcome Measure: Mortality rates for coronary heart disease (CHD), stroke, and the 7 most common cancers in the United Kingdom.

Results: A total of 46 136 people with SMI and 300 426 without SMI were selected for the study. Hazard ratios (HRs) for CHD mortality in people with SMI compared with controls were 3.22 (95% confidence interval [CI], 1.99-5.21) for people 18 through 49 years old, 1.86 (95% CI, 1.63-2.12) for those 50 through 75 years old, and 1.05 (95% CI, 0.92-1.19) for those older than 75 years. For stroke deaths, the HRs were 2.53 (95% CI, 0.99-6.47) for those younger than 50 years, 1.89 (95% CI, 1.50-2.38) for those 50 through 75 years old, and 1.34 (95% CI, 1.17-1.54) for those older than 75 years. The only significant result for cancer deaths was an unadjusted HR for respiratory tumors of 1.32 (95% CI, 1.04-1.68) for those 50 to 75 years old, which lost statistical significance after controlling for smoking and social deprivation. Increased HRs for CHD mortality occurred irrespective of sex, SMI diagnosis, or prescription of antipsychotic medication during follow-up. However, a higher prescribed dose of antipsychotics predicted greater risk of mortality from CHD and stroke.

Conclusions: This large community sample demonstrates that people with SMI have an increased risk of death from CHD and stroke that is not wholly explained by antipsychotic medication, smoking, or social deprivation scores. Rates of nonrespiratory cancer mortality were not raised. Further research is required concerning prevention of this mortality, including cardiovascular risk assessment, monitoring of antipsychotic medication, and attention to diet and exercise.

Arch Gen Psychiatry. 2007;64:242-249

Zusammenfassung

- Verminderte Lebenserwartung bei Schizophrenie, Ursachen:
  - Kardiovaskulär
  - Malignome
  - Suizid
  - Selten plötzlicher Herztod, Agranulozytose, Myokarditis, …
  - psychosoziale und krankheitseigene Faktoren?
- Rolle der NL:
  - Vermehrung kardiovaskulärer Risikofaktoren (Substanzabhängig!)
  - Verminderte Suizidrate unter Clozapin
  - plötzlicher Herztod unter Typika und Atypika (weitere Medikamente)