

# Therapiealgorithmen in der Depressionsbehandlung - Das Berliner Algorithmusprojekt -

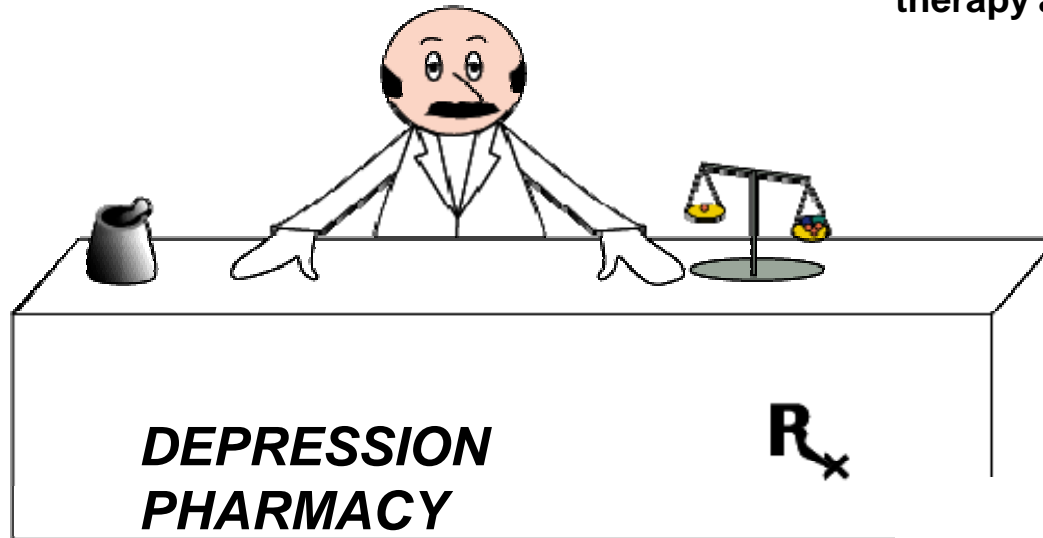
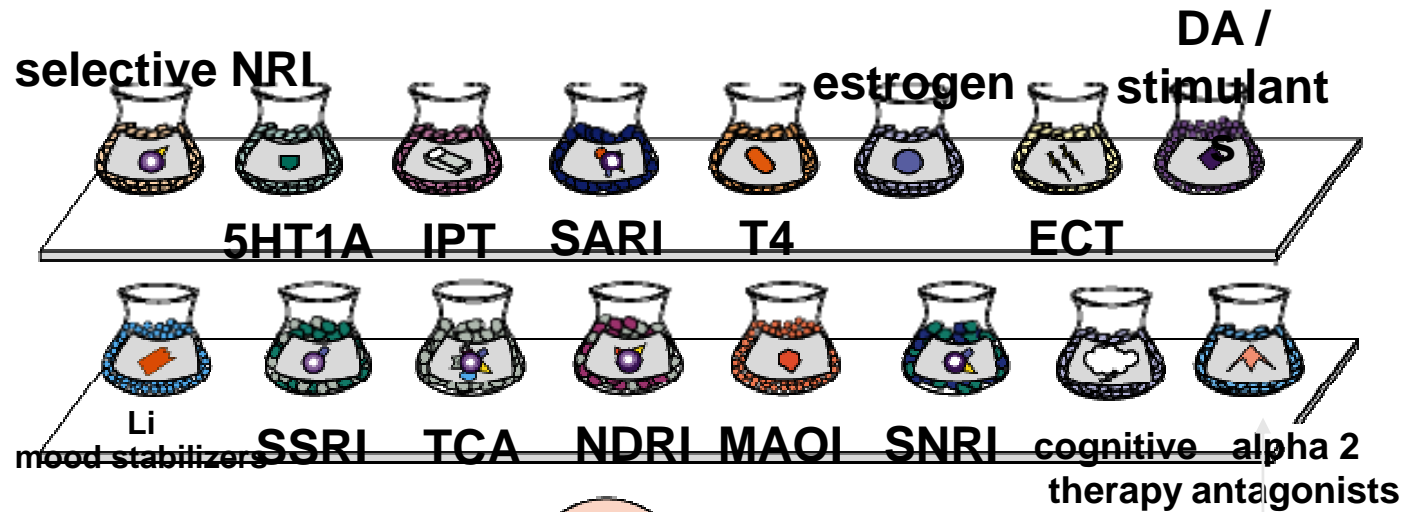
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München  
05.11.2009

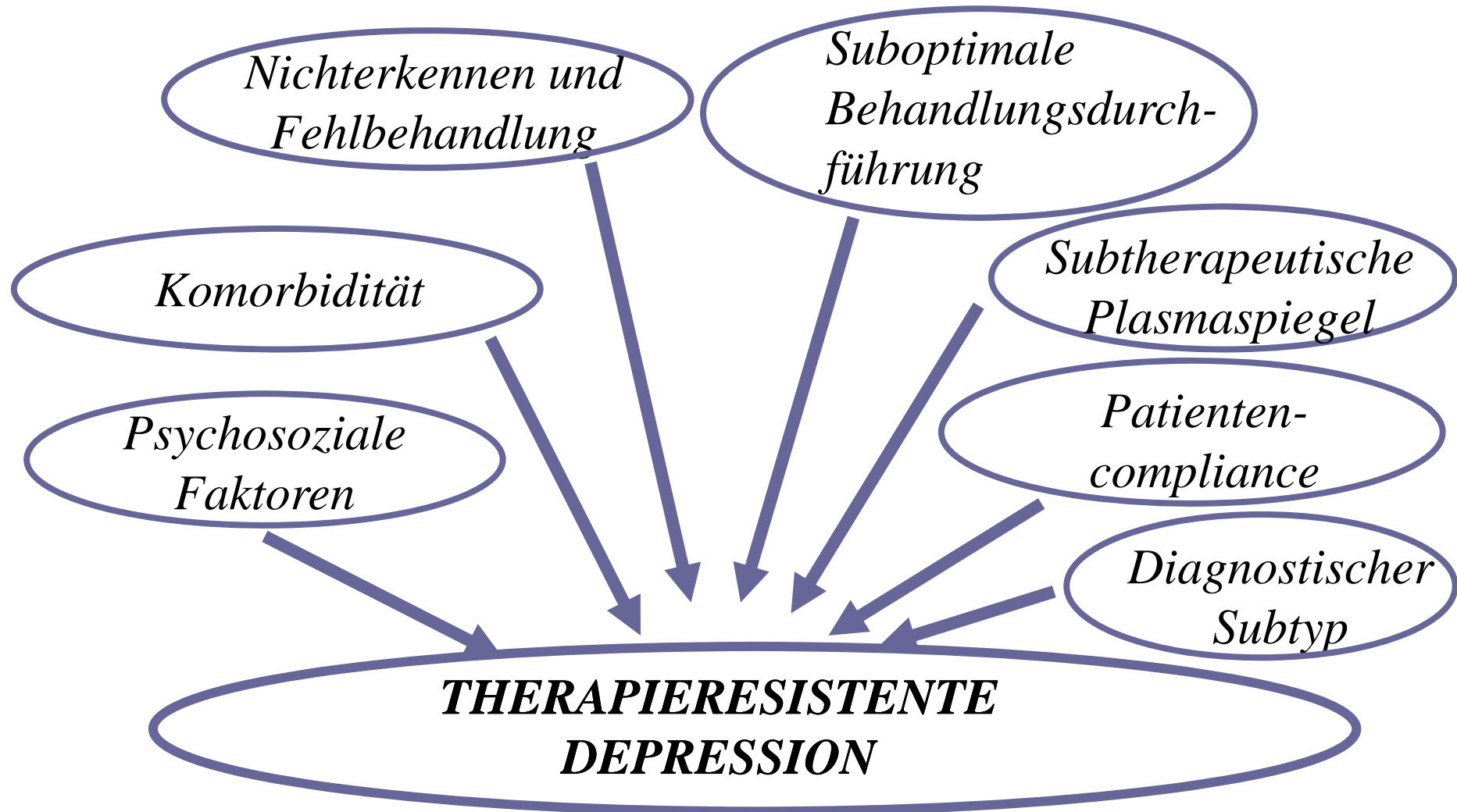


# Hintergrund



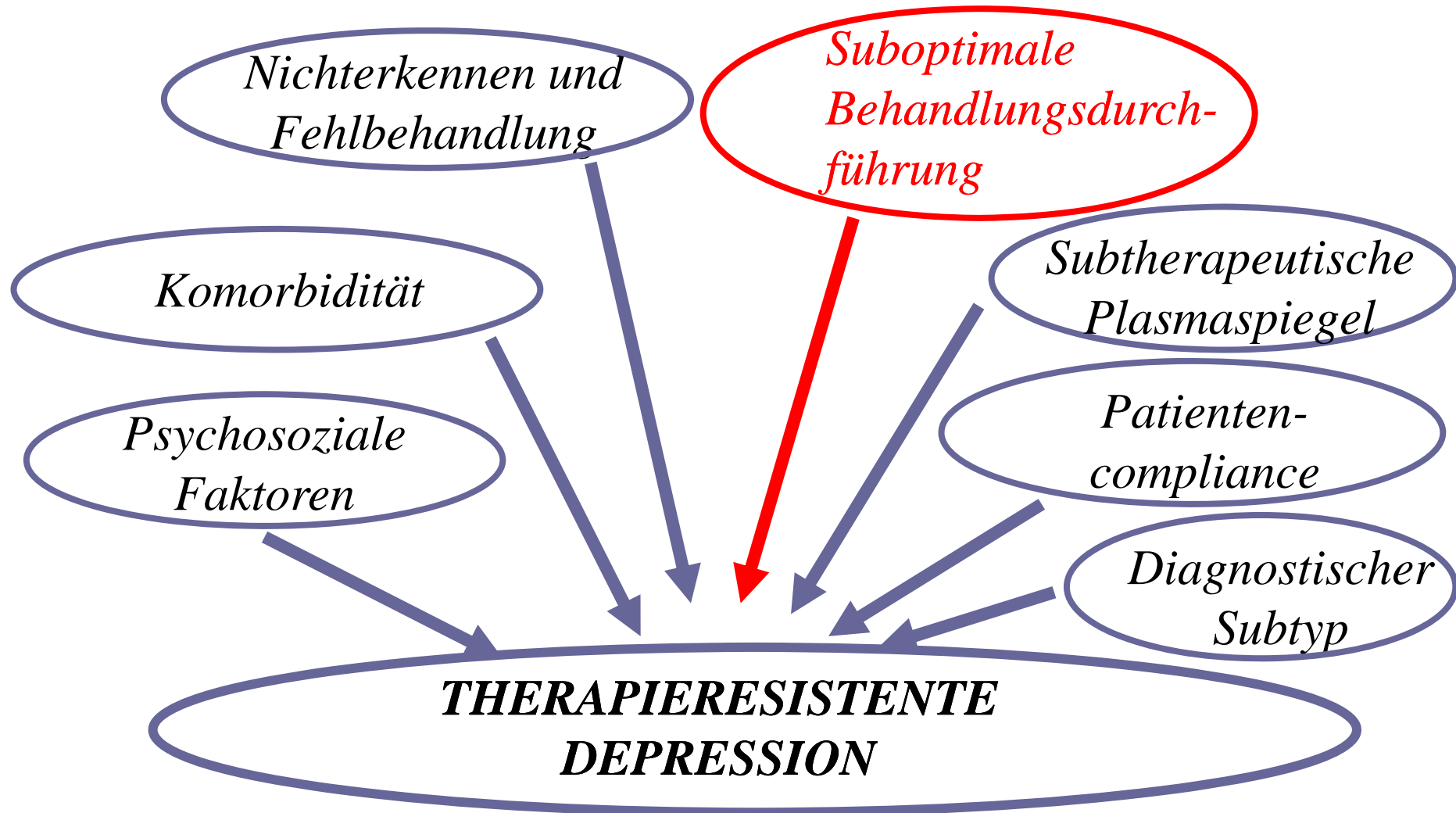


## Hintergrund





## Hintergrund





### Suboptimale Behandlungsdurchführung ?

- ▶ wahllos aneinander gereihte und unkontrolliert oder inadäquat vorgenommenen Therapien
- ▶ unzureichende Behandlungsdauer und Dosierung oder fehlende Nutzung von Therapiestrategien, die bei Therapieresistenz empfohlen werden



## Hintergrund

# Therapiealgorithmen



klar formulierte Behandlungsprotokolle  
mit standardisierten Handlungsanweisungen  
für therapeutische Entscheidungen

- falls eine adäquat durchgeführte Strategie nicht den zuvor definierten Behandlungserfolg erzielt

## Ziel:

Verbesserung von Therapieergebnis und -qualität



## The German Algorithm Project, GAP

1990-92	Anwendungsbeobachtung
GAP1	
1997-2000	Randomisierte kontrollierte Monozenterstudie („Berliner Stufenplanstudie“)
GAP2	
2000 - 2005	Randomisierte kontrollierte Multizenterstudie (Algorithmusstudie, Kompetenznetz Depression)
GAP3	

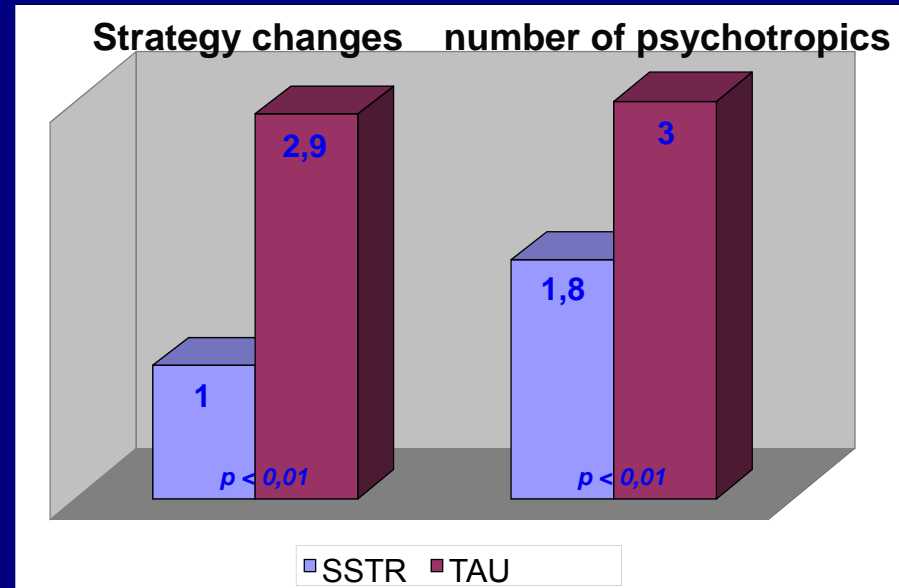
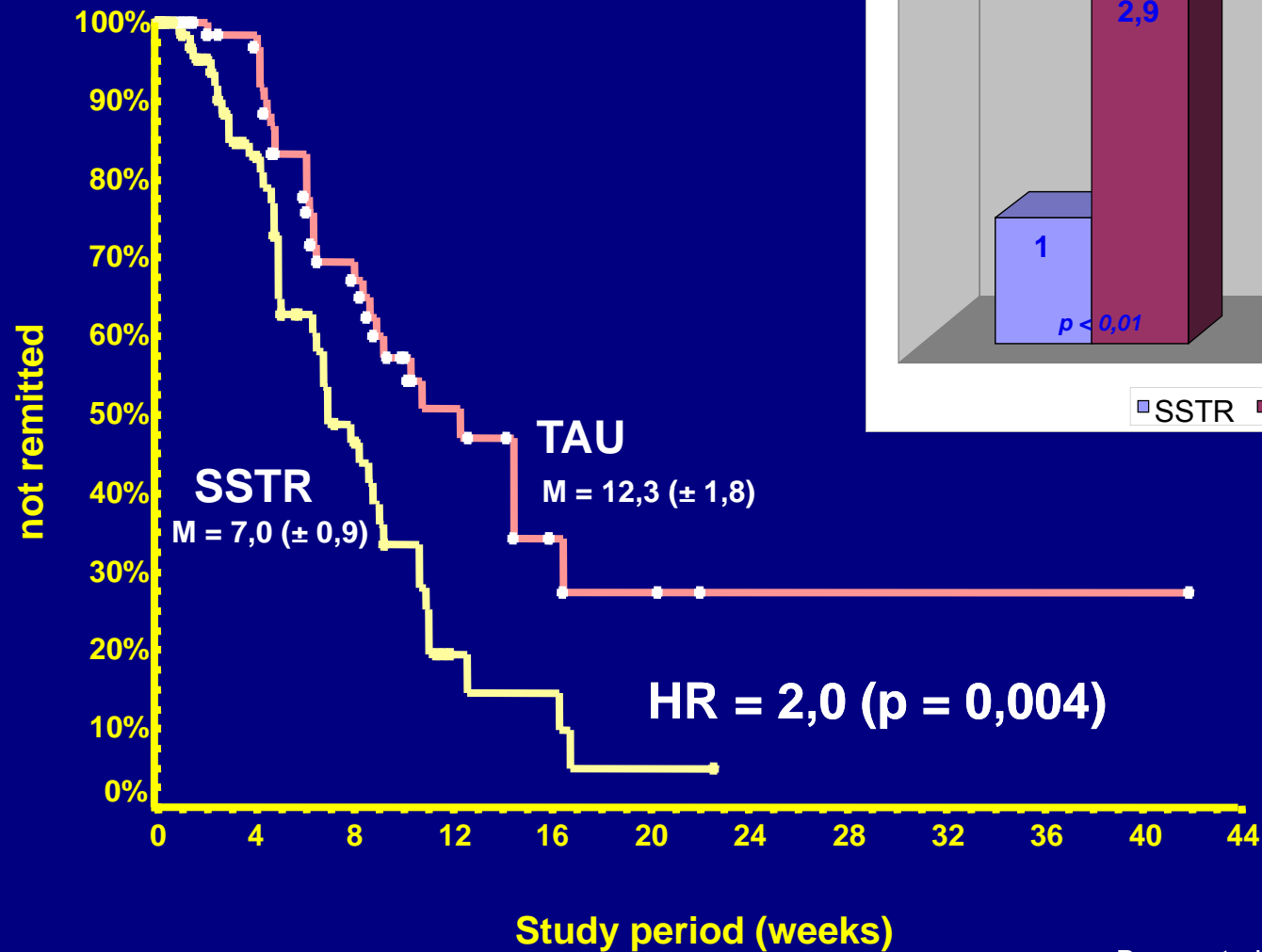


## Phase II

Randomisierte kontrollierte *Monozenterstudie*  
(„Berliner Stufenplanstudie“)

# Survival Analysis

Stufenplan (SSTR) = 74,  
treatment as usual (TAU) = 74





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## The German Algorithm Project - GAP3

### Phase III

Randomisierte kontrollierte *Multizenterstudie*  
„Algorithmusstudie“

Kompetenznetz Depression



# The German Algorithm Project - GAP3

## Methoden:

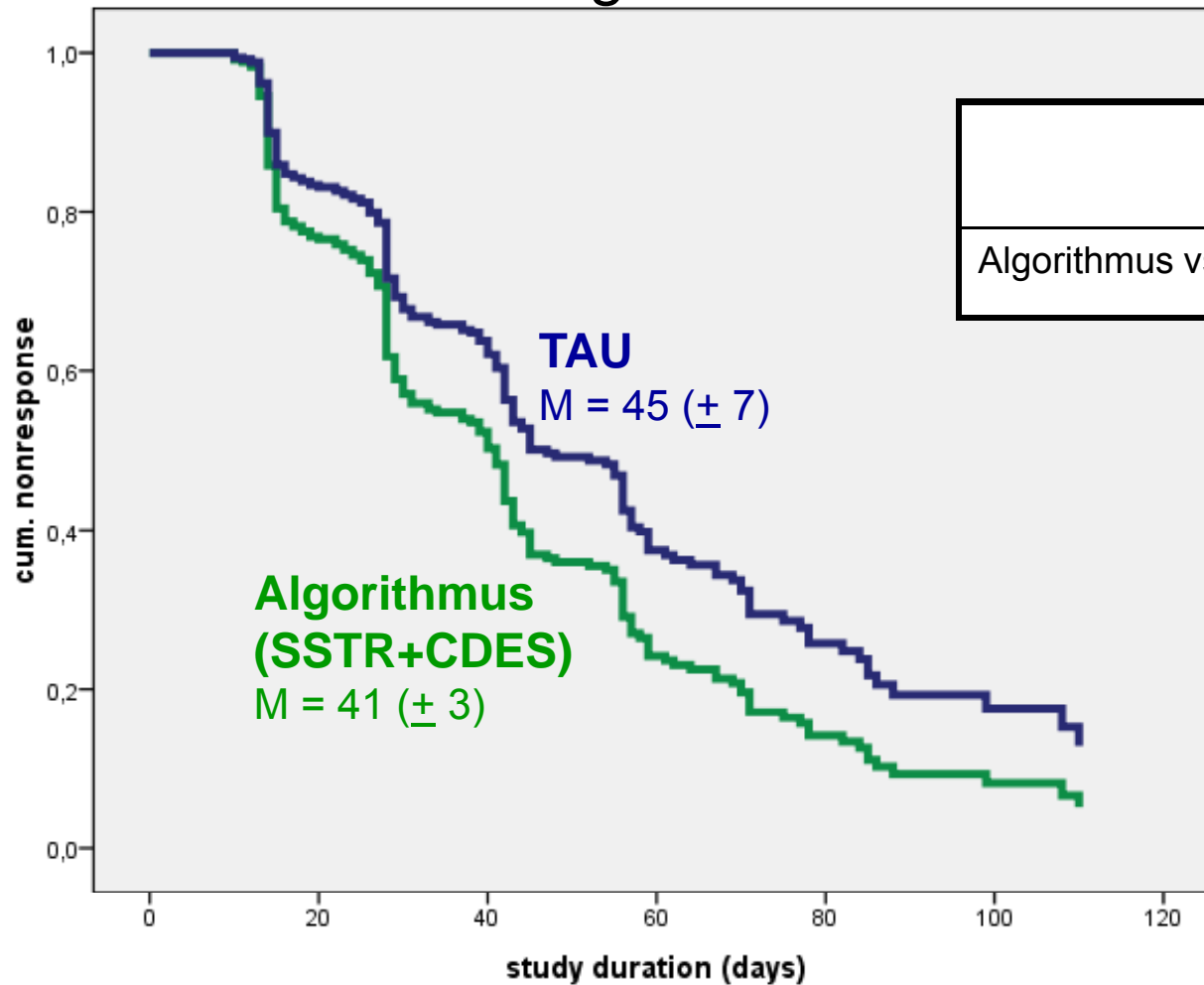
- 5-armige, randomisierte, kontrollierte, multizentrische Studie
- **SSTR**: Vergleich 3 second-step Strategien
- **CDES**: Computergestützter Algorithmus
- **TAU**: treatment as usual
- Evaluation: Hamilton Depression Rating Scale (HAMD-21)
- Remission:  $HAMD-21 \leq 9$
- $N = 429$

week	SSTR (I/1)	SSTR (I/2)	SSTR (I/3)	CDES (II)	TAU (III)		
0	Discontinuation period			Software-based pharmacotherapy COMPUTERIZED DOCUMENTATION - AND EXPERT SYSTEM	Free selection of treatment TREATMENT AS USUAL		
1	Antidepressant monotherapy						
2							
3							
4							
5	Lithium augmentation	High-dose antidepressant monotherapy	Change of drugs: antidepressant monotherapy				
6							
7	Lithium monotherapy	Lithium augmentation	Lithium augmentation				
8							
9	MAO-inhibitor	Lithium monotherapy	Lithium monotherapy				
10							
11	High-dose MAO-inhibitor	MAO-inhibitor	MAO-inhibitor				
12							
13	ECT	alternative: Ultra-high-dose MAO-inhibitor	High-dose MAO-inhibitor			High-dose MAO-inhibitor	
14							
15	T3 augmentation	ECT	alternative: Ultra-high-dose MAO-inhibitor			ECT	alternative: Ultra-high-dose MAO-inhibitor
16							
17	T3 augmentation	ECT	T3 augmentation			T3 augmentation	
18							
19			T3 augmentation			T3 augmentation	
20							



## The German Algorithm Project - GAP 3

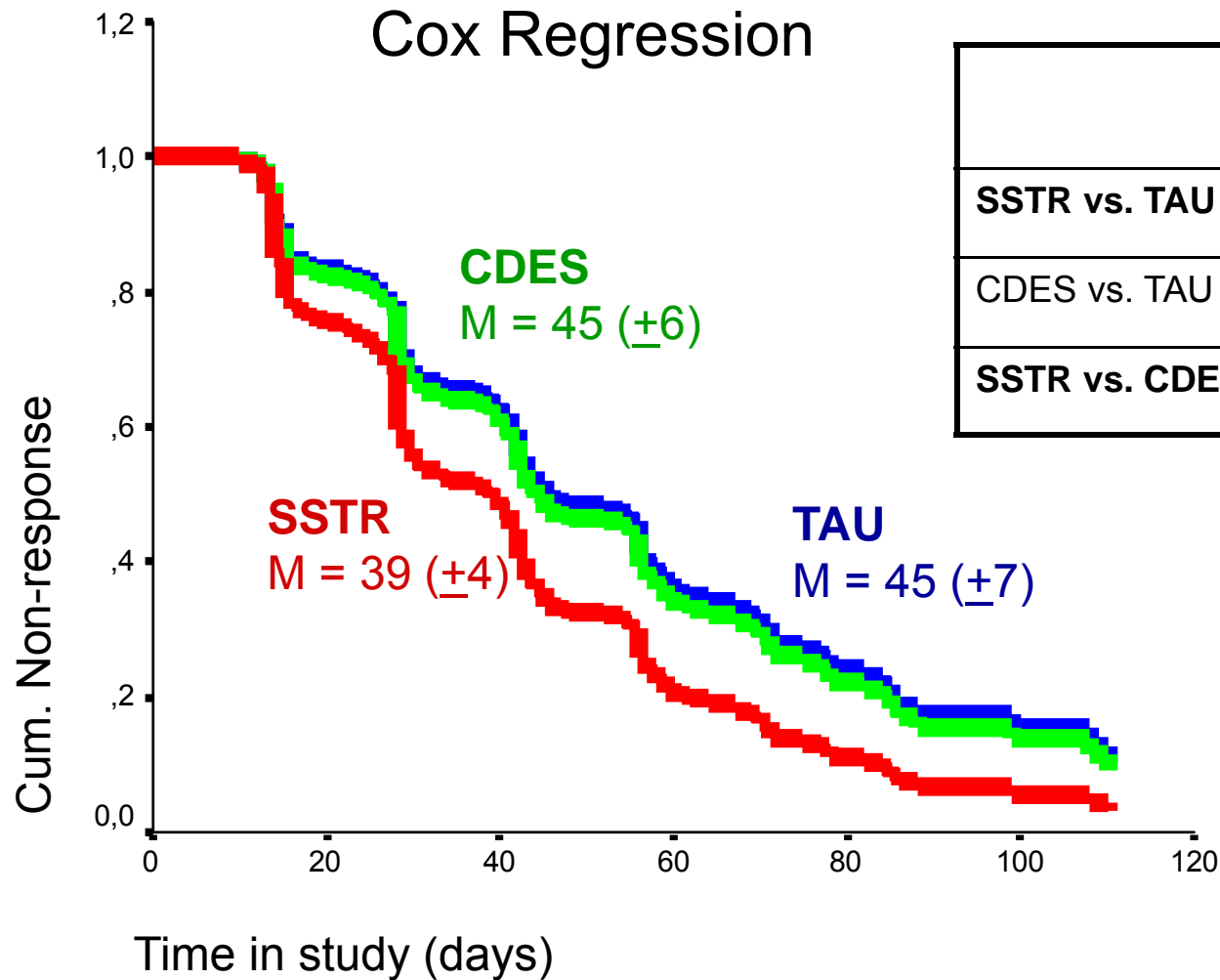
### Cox Regression



	Wald	Hazard-Ratio	p
Algorithmus vs. TAU	4.601	1.44	.032



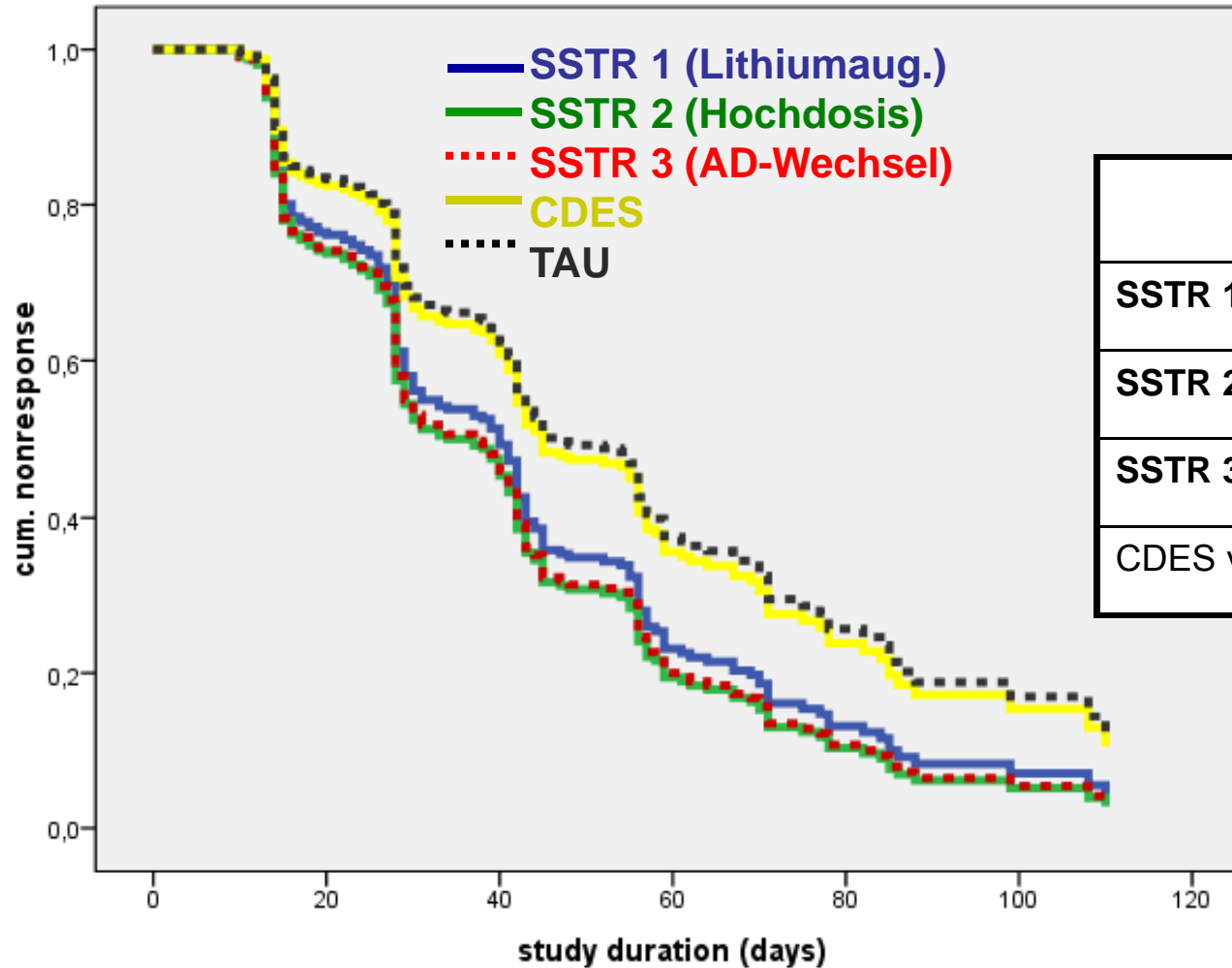
## The German Algorithm Project - GAP 3



	Wald	Hazard-Ratio	p
<b>SSTR vs. TAU</b>	<b>5.718</b>	<b>1.53</b>	<b>.017</b>
CDES vs. TAU	.006	1.02	.939
<b>SSTR vs. CDES</b>	<b>4.982</b>	<b>1.51</b>	<b>.026</b>



## The German Algorithm Project - GAP 3

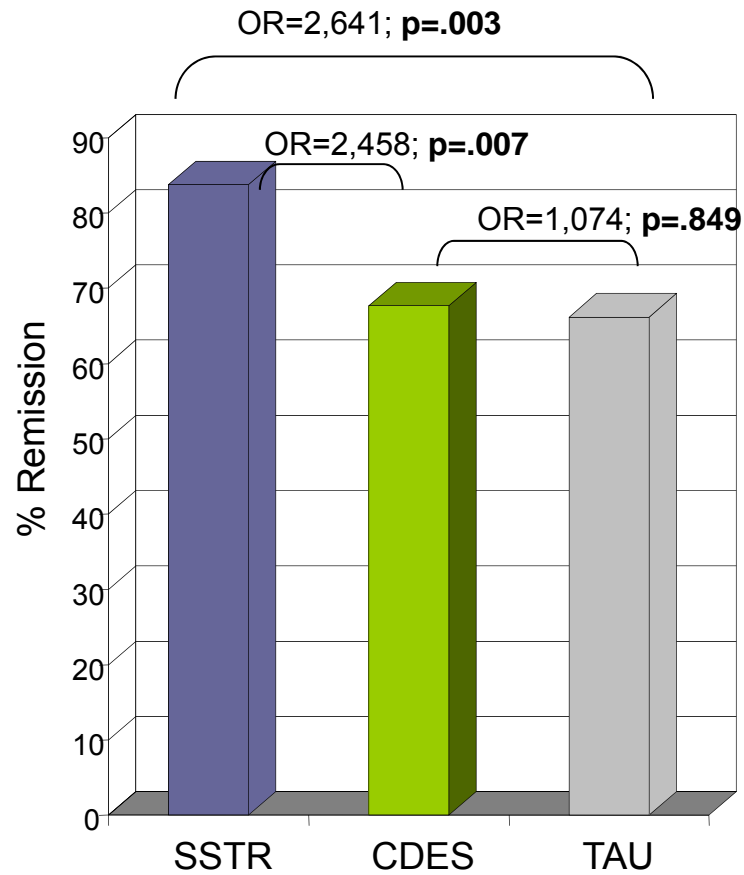


	Hazard-Ratio	p
SSTR 1 vs. TAU	1.494	.055
SSTR 2 vs. TAU	1.671	.014
SSTR 3 vs. TAU	1.643	.018
CDES vs. TAU	1.055	.811

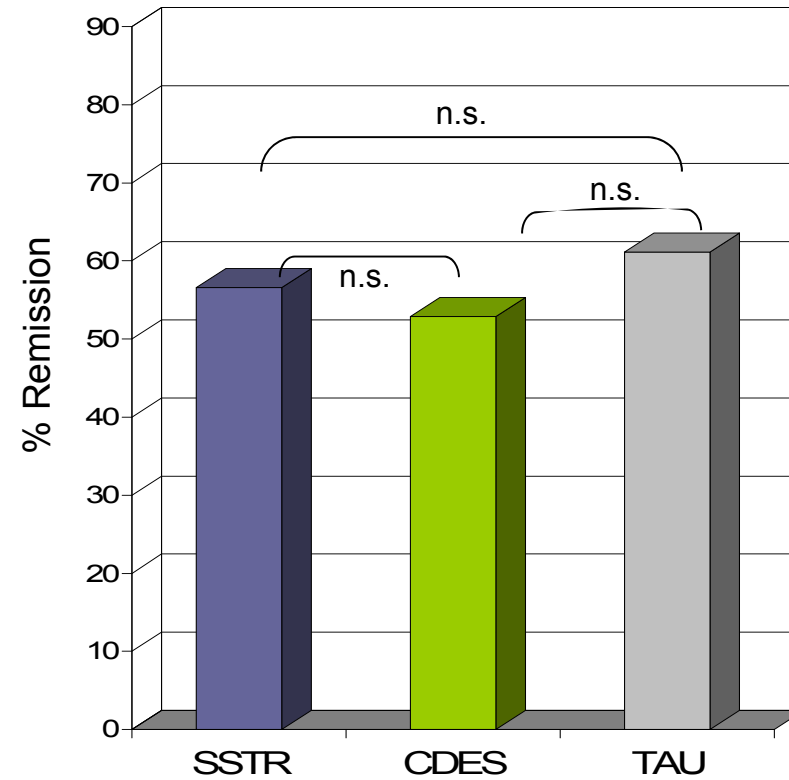


## SSTR exposition enhances clinical outcome at discharge

Discharge



1-year follow up





## GAP3: Kosten-Effektivitäts-Analyse

### Kosten-Effektivitäts-Analyse für die Studiendauer (ITT)

	SSTR (n=266)	TAU (n=84)	Statistic significance	Total (n=350)
average hospital-costs	<b>6 406 €</b> (± 4 951 €)	<b>8 189 €</b> (± 6 282 €)	<b>p=0.008</b>	6 834 € (± 5 346 €)
remission rate	0.58	0.50		0,56
costs / remission	<b>11 064 €</b>	<b>16 379 €</b>		12 203 €
medication-costs / remission	187 €	247 €		204 €



Welche Patienten brauchen Stufenpläne ?



....alle!

⇒ Keine Interaktion zwischen soziodemographischen oder klinischen Subtypen und Therapiemodus

Interaction with “diagnosis (F32/F33)“

	Wald	Hazard-Ratio	p
SSTR vs. TAU	8.142	1.949	.004
CDES vs. TAU	.463	1.215	.496
CDES vs. SSTR	4.223	.624	.040
diagnosis	4.867	2.006	.027
<b>diagnosis * group</b>	<b>2.808</b>		<b>.246</b>

Interaction with „age“

	Wald	Hazard-Ratio	p
SSTR vs. TAU	5.637	3.631	.018
CDES vs. TAU	2.377	2.632	.123
CDES vs. SSTR	.670	.690	.413
age	1.995		.369
<b>age * group</b>	<b>3.344</b>		<b>.502</b>

Interaction with “personality disorder“

	Wald	Hazard-Ratio	p
SSTR vs. TAU	7.11	1.596	.008
CDES vs. TAU	.051	1.051	.822
CDES vs. SSTR	5.358	1.518	.021
Personality disorder	0.243	1.125	.622
<b>Personality disorder * group</b>	<b>1.723</b>		<b>.423</b>

Interaction with “gender“

	Wald	Hazard-Ratio	p
SSTR vs. TAU	3.810	1.585	.051
CDES vs. TAU	.083	.922	.773
CDES vs. SSTR	6.730	.582	.009
gender	.341	.835	.560
<b>gender * group</b>	<b>1.053</b>		<b>.591</b>



### Interaction with “anxious depression“

	Hazard-Ratio	p
SSTR vs. TAU	1.53	.015
CDES vs. TAU	1.01	.977
SSTR vs. CDES	1.52	.020
non-anxious depression	1.66	.000
<b>anxiousness* group</b>		<b>.890</b>

### Interaction with „psychotic depression“

	Wald	Hazard-Ratio	p
SSTR vs. TAU	5.451	1.519	.020
CDES vs. TAU	.055	1.055	.815
CDES vs. SSTR	3.845	1.440	.050
Psychotic depression	1.523	.285	.217
<b>Psychotic depression * group</b>	<b>1.737</b>		<b>.420</b>

### Interaction with “suicide attempt“

	Hazard-Ratio	p
SSTR vs. TAU	8.620	.003
CDES vs. TAU	.252	-.616
SSTR vs. CDES	1.507	.025
Suicide attempt	1.390	.016
<b>Suicide attempt* group</b>		<b>.797</b>

### Interaction with “HAMD baseline“

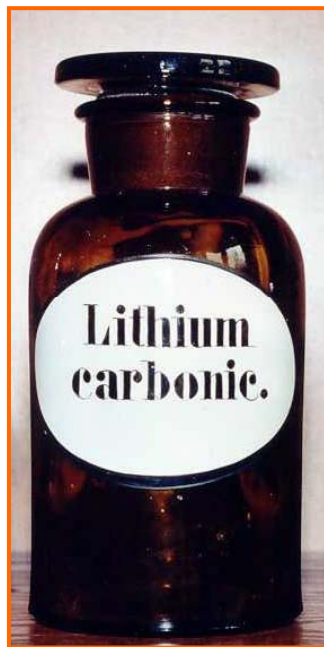
	Wald	Hazard-Ratio	p
SSTR vs. TAU	4.106	1.431	.043
CDES vs. TAU	.104	.747	.930
CDES vs. SSTR	5.707	1.538	.017
HAMD baseline	18.587	.949	.000
<b>HAMD * group</b>	<b>.506</b>		<b>.776</b>



# Pharmakogenetik als personalisierte Wegweiser in Therapiealgorithmen ?



## Which genotype is associated with response to lithium augmentation ?



Prediction of lithium augmentation response

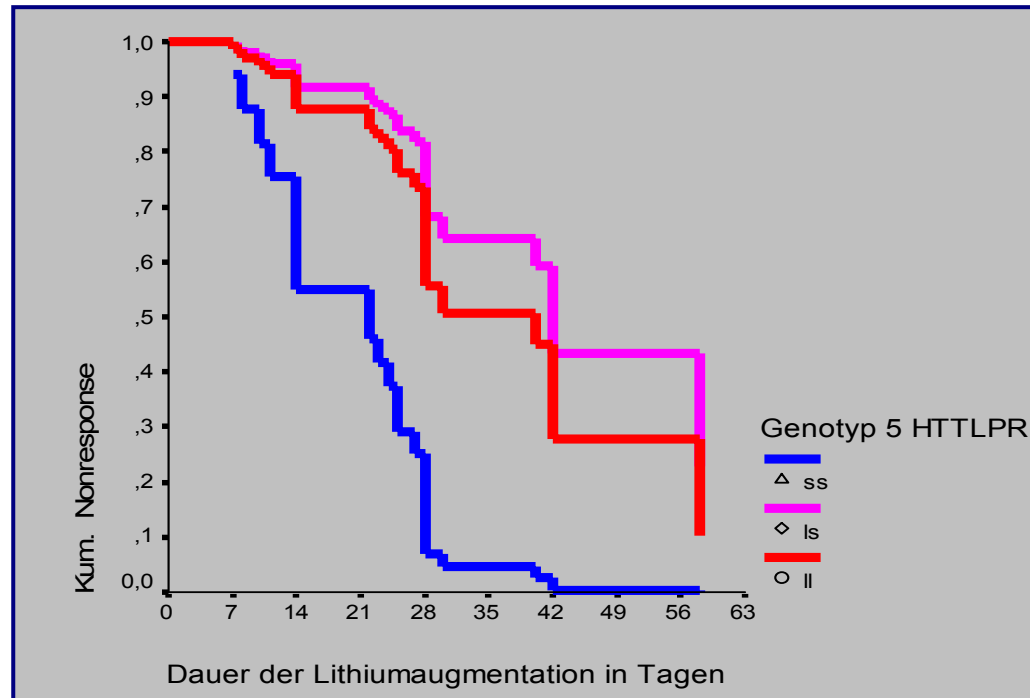
5HTTLPR

GSK3-beta

week	SSTR (I/1)	SSTR (I/2)	SSTR (I/3)
0	Discontinuation period		
1	Antidepressant monotherapy		
3			
4			
5	Lithium augmentation	High-dose antidepressant monotherapy	Change of drugs: antidepressant monotherapy
6			
7			
8			



## 5HTTLPR and lithium augmentation response



### Cox regression- survival analysis for factor 5HTTLPR

N=50

→ duration of lithium  
augmentation to  
remission (BRMS  $\leq$  7)

remission rates:

Overall: 27/50 (54%)

▶ ss : 7/9 (78%)

▶ ls: 9/19 (47%)

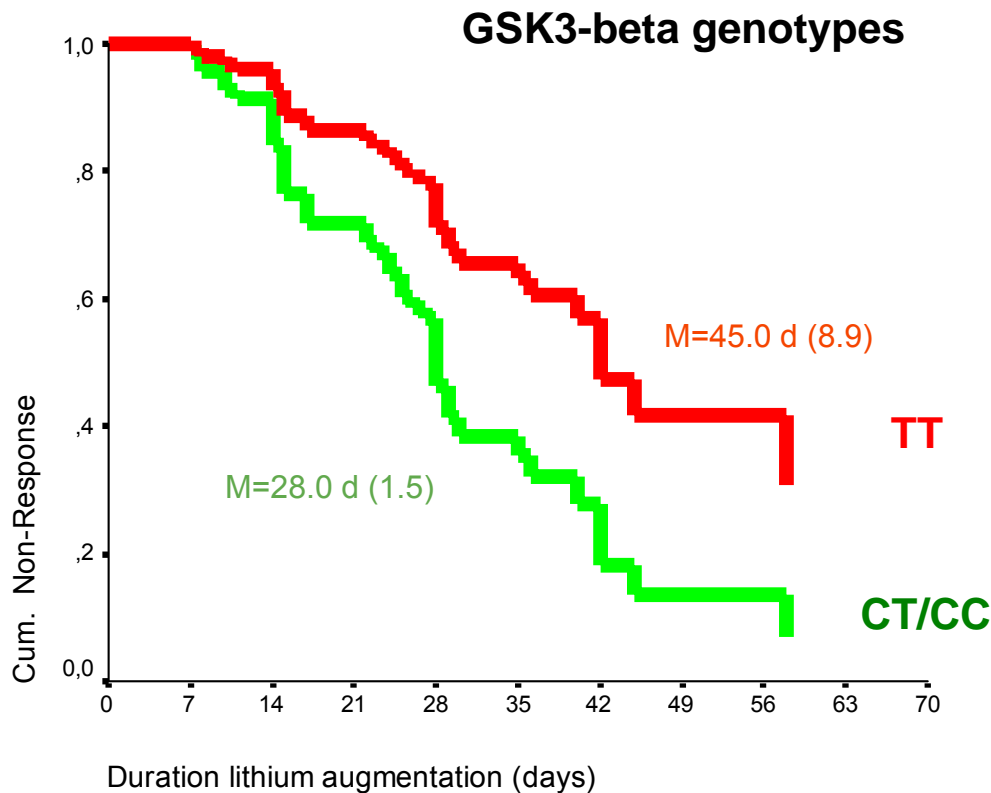
▶ ll: 11/22 (50%)

In the modell	Wald	p-value	Hazard-Ratio	SD for HR
5-HTTLPR ss vs ls	8,59	0,005	6,9	1,9-25,0
5-HTTLPR ss vs ll	7,98	0,003	4,5	1,6-12,8
Bi- vs unipolar depression	3,30	0,070	2,8	0,9-8,7
Psychotic features no vs yes	3,37	0,066	4,2	0,9-20,3

Stamm, Adli et al., Psychiatric Gen, 2008



## Response to lithium augmentation treatment in depression is associated with polymorphisms of glycogen synthase kinase 3-beta (GSK3-beta) gene (50T/C-SNP)



GSK3-beta			
genotype	CT	CC	TT
n	39	12	30
percent	47	14.5	36.1

### Statistics

**N=81**

#### Remission rates:

CC/CT 31/51 (60.8%)

TT 13/30 (43.3%)

#### Kaplan-Meier-Analysis:

Log Rank 5,88 p= ,0153

#### Cox Regression Analysis

p = .021 HR = 2.27

### Remission rates after 4 weeks

CC / CT: 56.25% (CC 60%, CT 55.2%)

TT: 31% (chi2=4.1; p=.04)

Covariates: GSK3 $\beta$ -genotype, age, sex, psychotic symptoms, personality disorder, unipolar/bipolar depression, severity of depression, antipsychotic medication



## Zusammenfassung und Schlussfolgerung

- SSTR führt zu besserem Therapieergebnis als CDES und TAU und verursacht geringere Kosten pro Remission als TAU
- Keine Interaktion soziodemographischer oder klinischer Subtypen und Therpaiemodus → Überlegenheit des SSTR gilt über alle Subtypen
- Vorgehen unter stärkerer Berücksichtigung von individuellem Verlauf und Vorgeschichte (CDES) ist nicht effektiver als TAU
- 5HTTLPR- and GSK3B -50T/C Varianten könnten Response auf Lithiumaugmentation in antidepressiva-resistenten Patienten im Stufenplan vorherhsagen
- Alle Patienten profitieren von SSTR, aber „personalisierte Navigation“ ist vermutlich nützlich



## German Algorithm Project – researchers

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### Statistics

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### Drug Monitoring

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### Health Economy

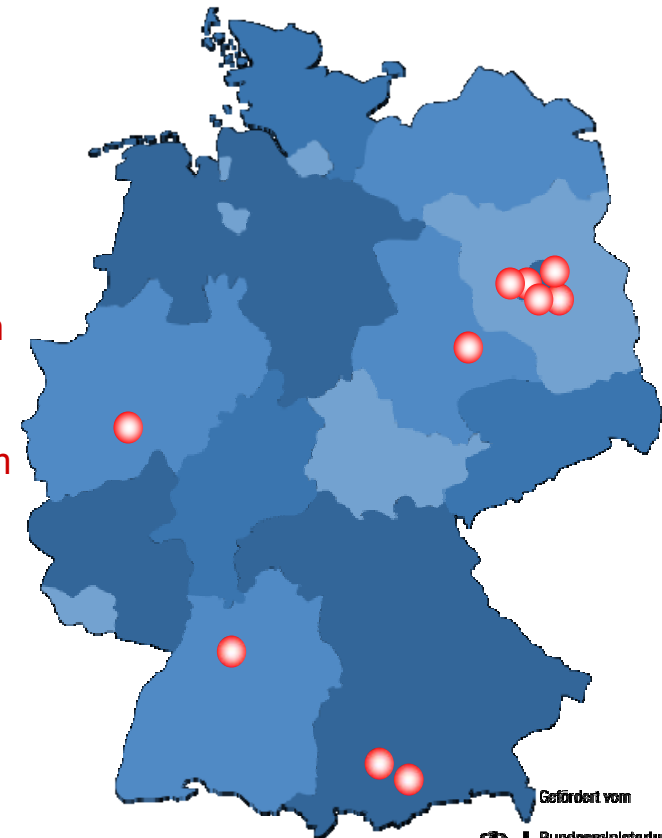
Thomas Reinhold, Berlin  
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### Pharmakogenetics

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Rolf Kaiser, Göttingen  
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### Wissenschaftliche Beratung

Externer Beirat des  
Kompetenznetz Depression





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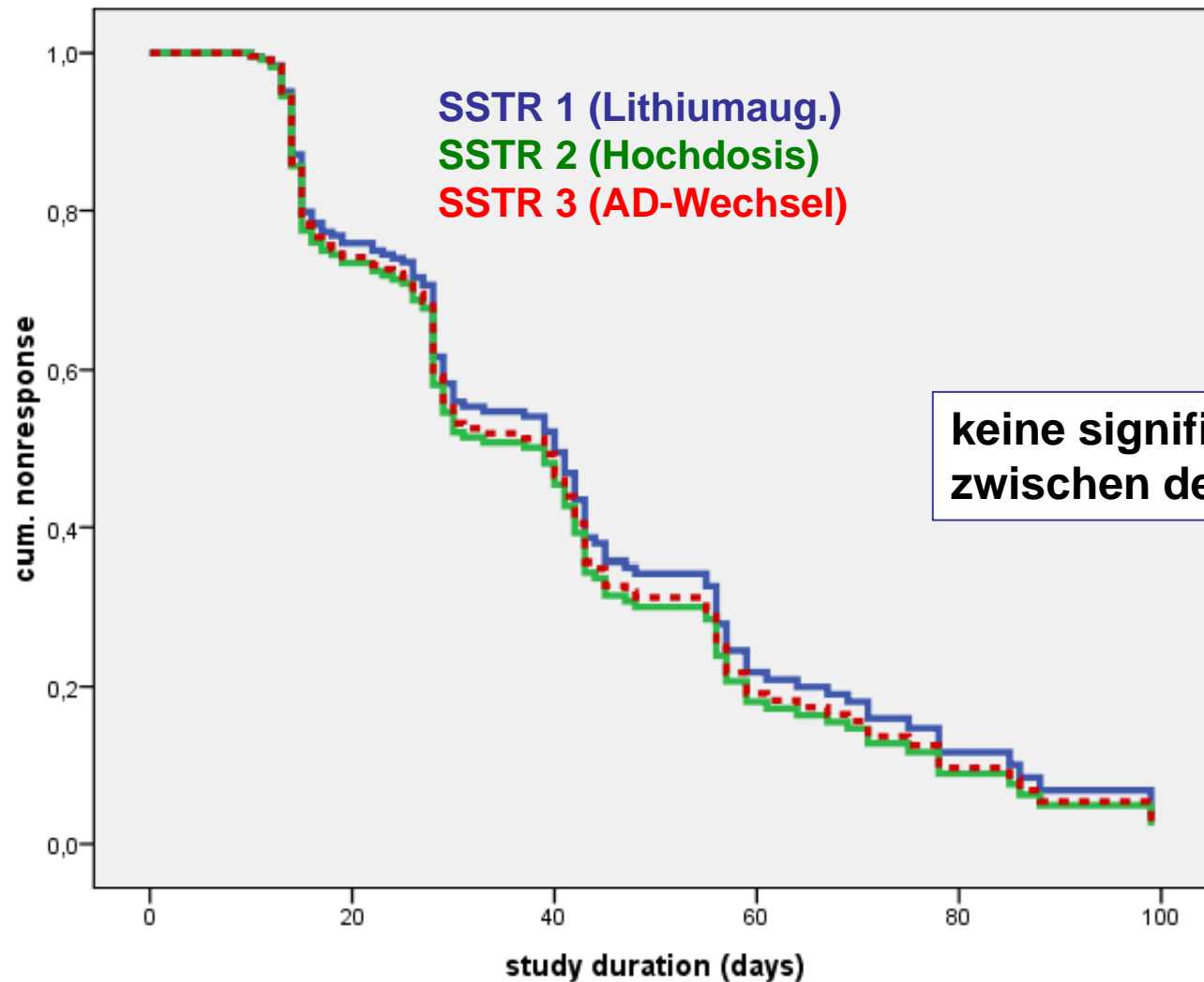
Charité – Universitätsmedizin Berlin  
Klinik für Psychiatrie und Psychotherapie

German Algorithm Project





## The German Algorithm Project - GAP 3



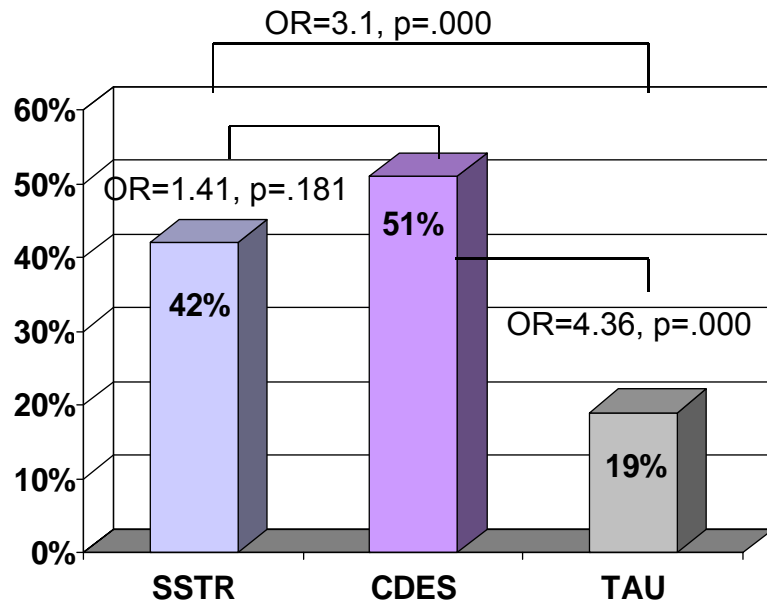
**keine signifikanten Unterschiede  
zwischen den Stufenplanarmen**

	Lithium Augmentation	Hochdosis	AD-Wechsel
Total (ab <b>Stufe 1</b> )	<b>86</b>	<b>91</b>	<b>89</b>
Remission in Stufe 1	39 (45.3%)	42 (46.2%)	39 (43.8%)
Drop in Stufe 1	25 (29.1%)	35 (38.5%)	36 (40.4%)
Total (ab <b>Stufe 2</b> )	<b>22</b> (25.6%)	<b>14</b> (15.4%)	<b>14</b> (15.7%)
Remission in Stufe 2	12	6	8
dropouts	6	1	1
Total (ab <b>Stufe 3</b> )	<b>3</b>	<b>7</b>	<b>5</b>
Remission in Stufe 3	0	4 Lithiumaug	4 Lithiumaug
dropouts	2	3	1
Total (ab <b>Stufe 4</b> )	<b>1</b>	<b>0</b>	<b>0</b>

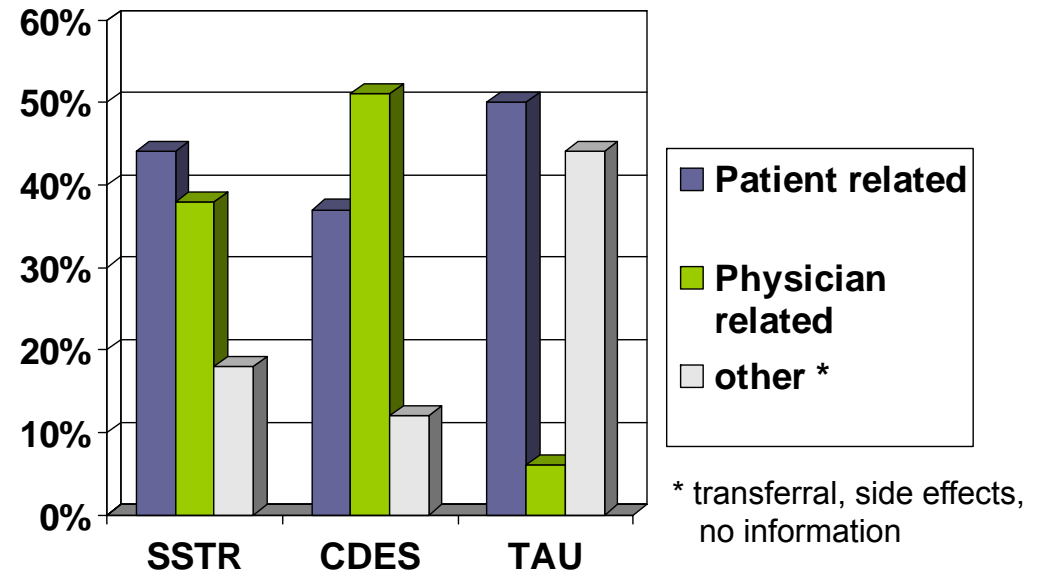


# Dropoutanalyse → Akzeptanz

## Dropout Raten



## Gründe für Dropout



keine sig. Unterschiede zwischen SSTR und CDES (Chi<sup>2</sup> = 12.286; p = .092)

N=475 were recruited  
gave their written  
consent and were  
randomized

N=46 dropped out  
after randomization

N=429 eligible for  
analysis

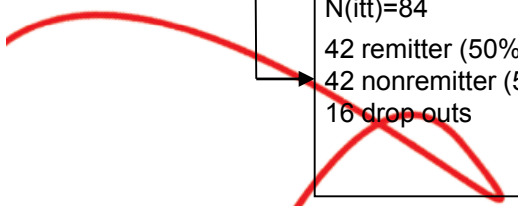
**SSTR**

N=266  
154 remitter (57.9%)  
112 drop outs (42.1%)

	Step 1 N(it)=266	Step 2 N=50 (18.8%)	Step 3 N=16 (6.0%)	Step 4 N=1 (0.4%)	Step 5 N=1 (0.4%)	Step 6 N=1 (0.4%)
	Remission N=120 (45.1%) Drop out N=96 (36.1%)	Remission N=26 (54.9%) Drop out N=8 (39.1%)	Remission N=8 (57.9%) Drop out N=7 (41.7%)	Remission N=0 Drop out N=0	Remission N=0 Drop out N=0	Remission N=0 Drop out N=1 (42.1%)
<b>Group I/1</b>	AD mono N=86 39 remitter 25 drop outs	Lithium augment. N=22 12 remitter	Lithium mono N=3 0 remitter 2 drop outs	MAO N=1 0 remitter 0 drop out	MAO high dose N=1 0 remitter 0 drop out	T3 augment. N=1 0 remitter 1 drop out
<b>Group I/2</b>	AD mono N=91 42 remitter 35 drop outs	High dose therapy N=14 6 remitter	Lithium augment. N=7 4 remitter			
<b>Group I/3</b>	AD mono N=89 39 remitter 36 drop outs	AD change N=14 8 remitter 1 drop out	Lithium augment. N=5 4 remitter 1 drop out			

<b>CDES</b>	before week 2	week 2	week 4	week 6	week 8	week 10	week 12	> week 12
N(it)=79	Remssion=0	Remssion=1	Remssion=10	Remssion=4	Remssion=7	Remssion=7	Remssion=7	Remssion=0
39 remitter (49.4%)		(19%)	(31.7%)	(36.8%)	(45.7%)	(48.2%)	(49.5%)	
40 drop outs (50.6%)	Drop out=5 (6.3%)	Drop out=11 (20.2%)	Drop out=7 (29.1%)	Drop out=10 (41.8%)	Drop out=2 (44.3%)	Drop out=0	Drop out=1 (45.6%)	Drop out=4 (50.7%)

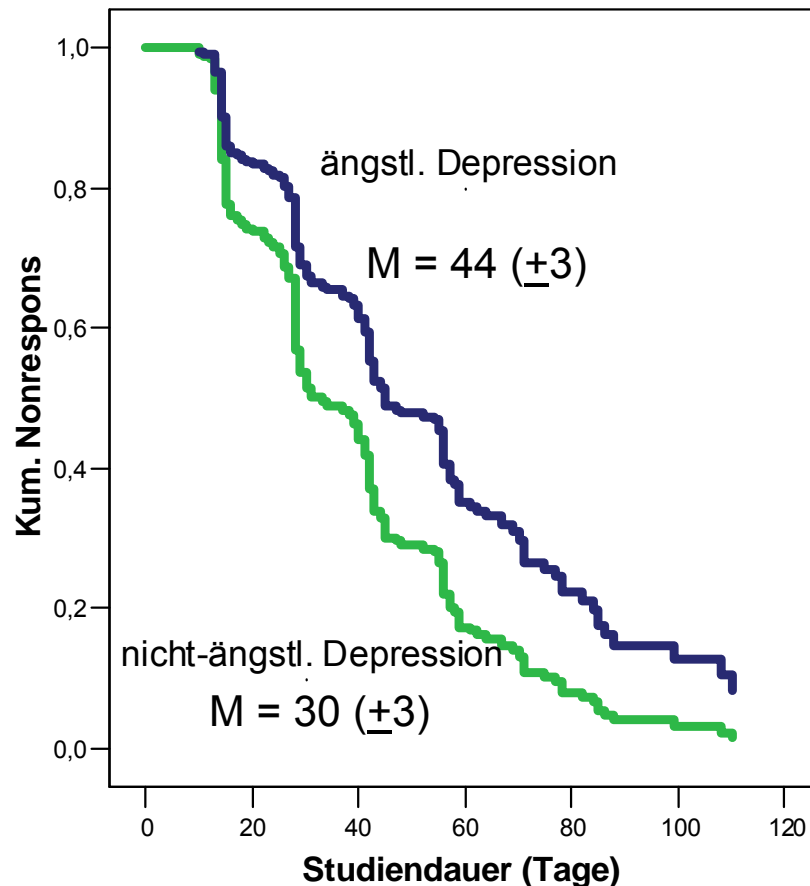
<b>TAU</b>	before week 2	week 2	week 4	week 6	week 8	week 10	week 12	week 16
N(it)=84	Remssion=0	Remssion=9	Remssion=12	Remssion=9	Remssion=3	Remssion=4	Remssion=2	Remssion=3
42 remitter (50%)		(10.7%)	(25%)	(35.7%)	(39.3%)	(44.1%)	(46.5%)	(50.1%)
42 nonremitter (50%)	Drop out=11 (13.1%)	Drop out=2 (15.5%)	Drop out=2 (17.9%)	Drop out=1 (19.1%)	Drop out=0	Drop out=0	Drop out=0	Drop out=0
16 drop outs								





# The German Algorithm Project, GAP 3

## Cox Regression, anxious vs. non-anxious depression



	Hazard-Ratio	p
<b>SSTR vs. TAU</b>	<b>1.53</b>	<b>.015</b>
CDES vs. TAU	1.01	.977
<b>SSTR vs. CDES</b>	<b>1.52</b>	<b>.020</b>
<b>ängstl. vs. nicht-ängstl. Depression</b>	<b>1.66</b>	<b>.000</b>
Art der Depression* Behandlungsarm		.890

### Remission rates:

Anxious depression: 107/220 (48.6%)

Non-anxious depression: 128/208 (61.5%)

$\chi^2 = 7.19$ ;  $p = .007$

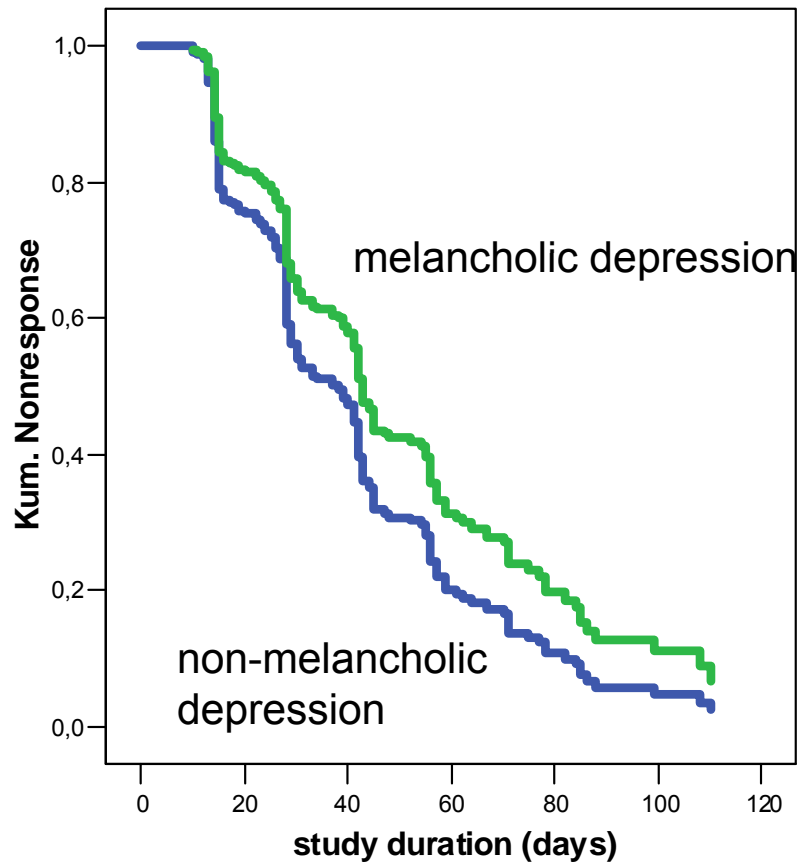
Wiethoff et al. submitted



## The German Algorithm Project, GAP 3

### Cox Regression, melancholic vs. non-melancholic depression

N=247/429 (57.6%), DSMIV



	Hazard-Ratio	p
<b>SSTR vs. TAU</b>	<b>1.84</b>	<b>.002</b>
CDES vs. TAU	1.03	.903
<b>SSTR vs. CDES</b>	<b>1.79</b>	<b>.004</b>
<b>melanchol. vs. non-melanchol. depression</b>	<b>1.38</b>	<b>.037</b>
Art der Depression* Behandlungsarm		.548

#### Remission rates:

melancholic depression: 138/247 (55.9%)

Non-mel. depression: 63/100 (63%)

$\chi^2 = 1.485$ ;  $p = .223$

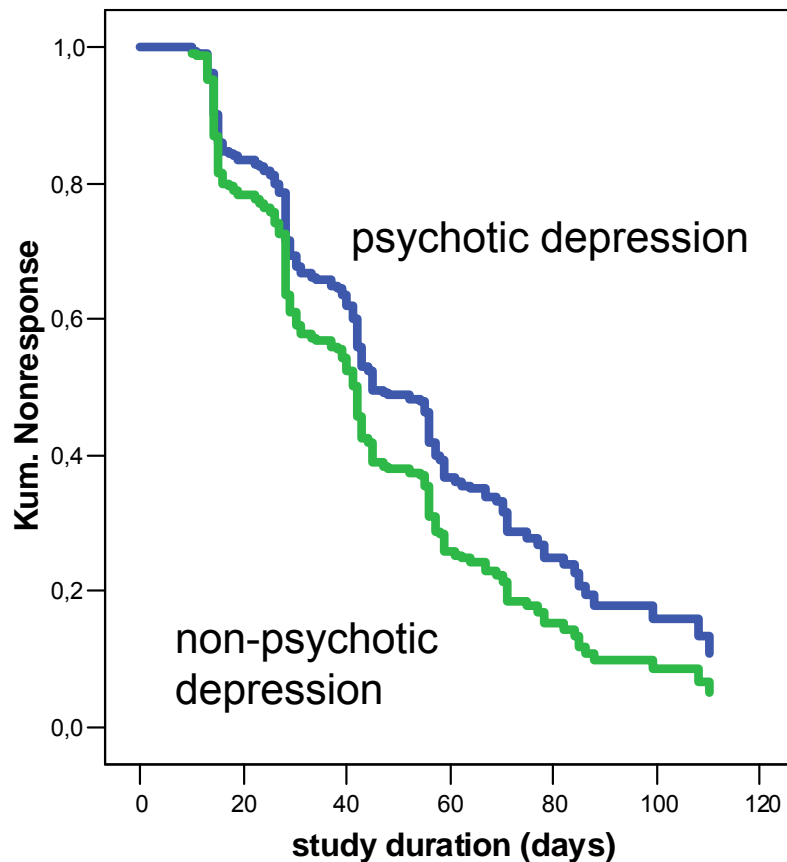
**Hohe Überschneidung mit anxious depression → 77%**



## The German Algorithm Project, GAP 3

### Cox Regression, psychotic vs. non-psychotic depression

N=28/429 (6,5%), ICD10



	Hazard-Ratio	p
<b>SSTR vs. TAU</b>	<b>1.52</b>	<b>.020</b>
CDES vs. TAU	1.06	.815
<b>SSTR vs. CDES</b>	<b>1.44</b>	<b>.050</b>
psychot. vs. non-psychot. depression	0.29	.217
Art der Depression* Behandlungsarm		.420

#### Remission rates:

psychotic depression: 17/28 (60.7%)

non-psychotic depression: 216/392 (55.1%)

chi<sup>2</sup> = 0.333; p = .564

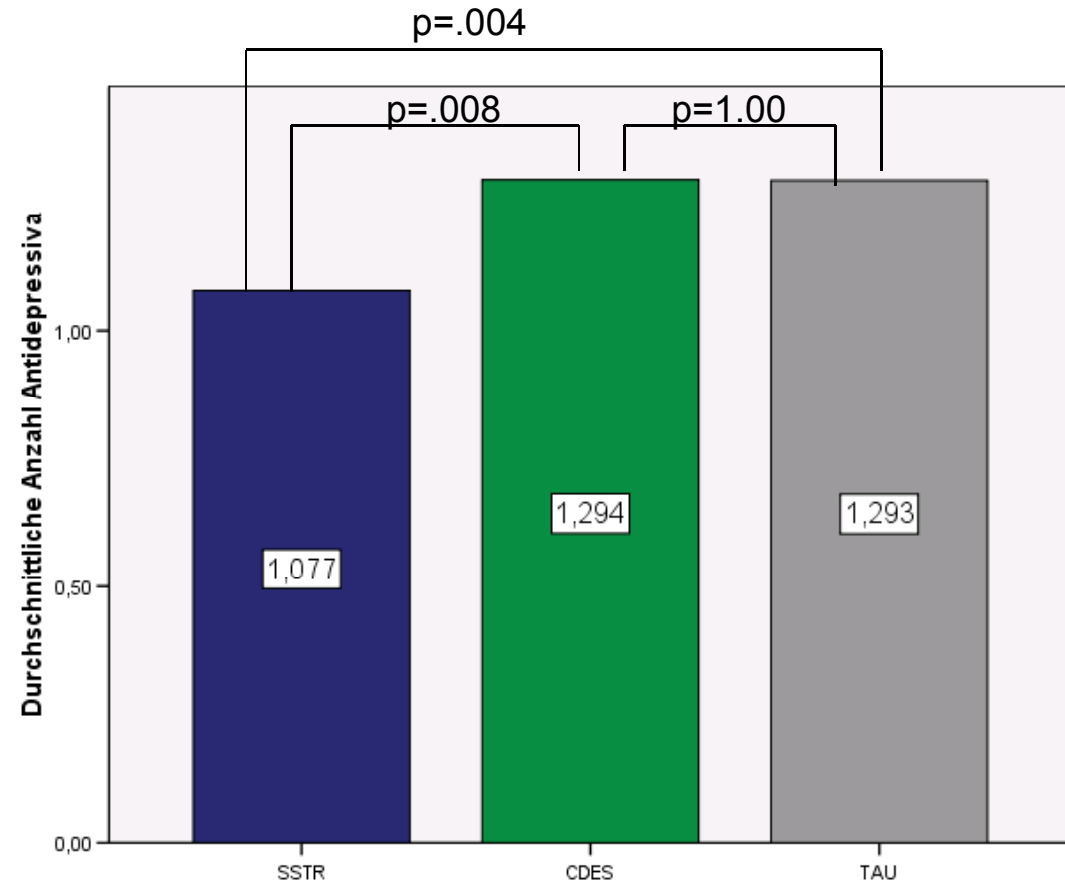
## Ergebnisse III:

*Keine Unterschiede zwischen SSTR, CDES und TAU:*

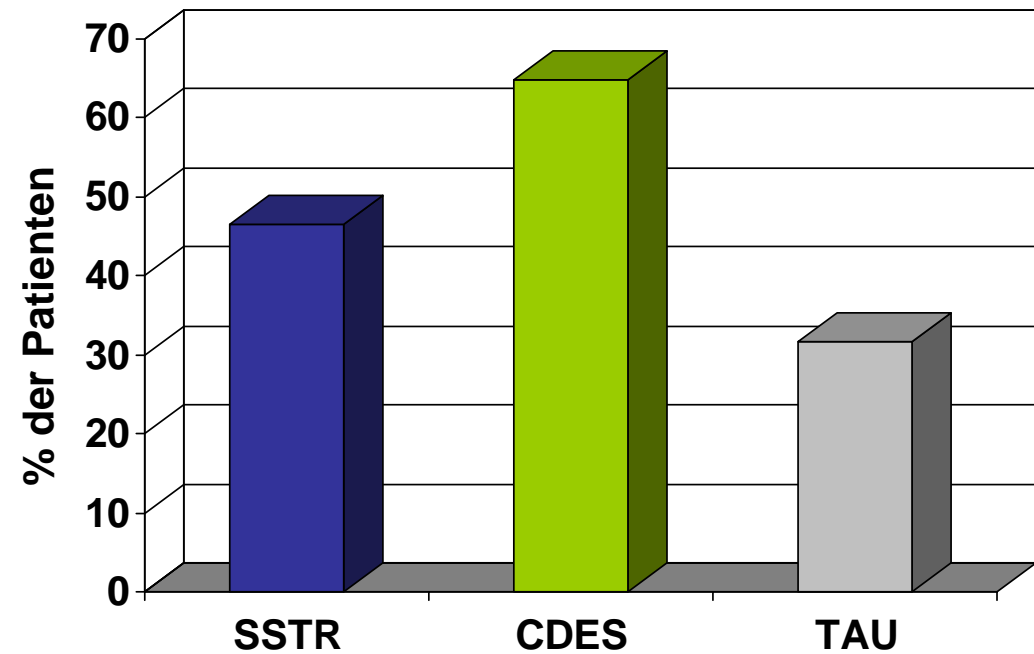
- in der Dosierung der Antidepressiva (DDD) ( $F=1.161$ ,  $p=.329$ )
- in der generellen Verschreibung, der Anzahl, Dosierung oder Dauer der Behandlung mit Tranquilizern oder Antipsychotika
- in der Anzahl unterschiedlicher Substanzen
- in der Anzahl der Strategiewechsel



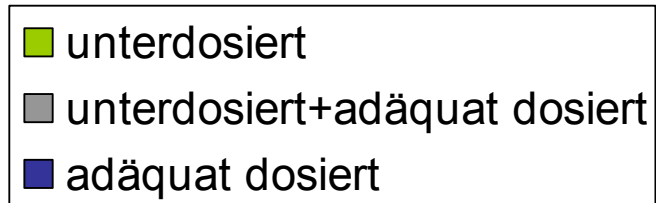
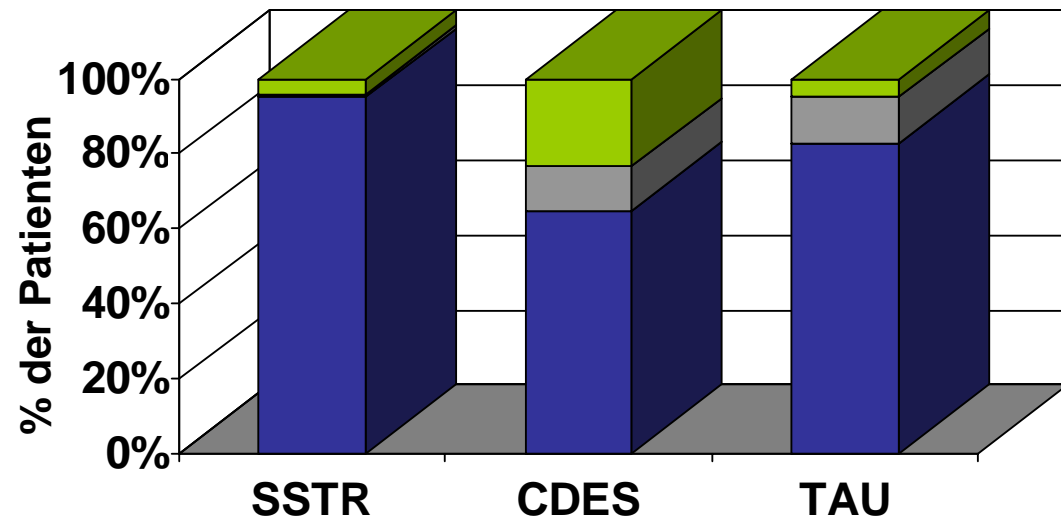
SSTR Patienten brauchen unter Studien- bedingungen weniger Antidepressiva zum Erreichen der Remission als TAU und CDES (F=8,241; p=.000)

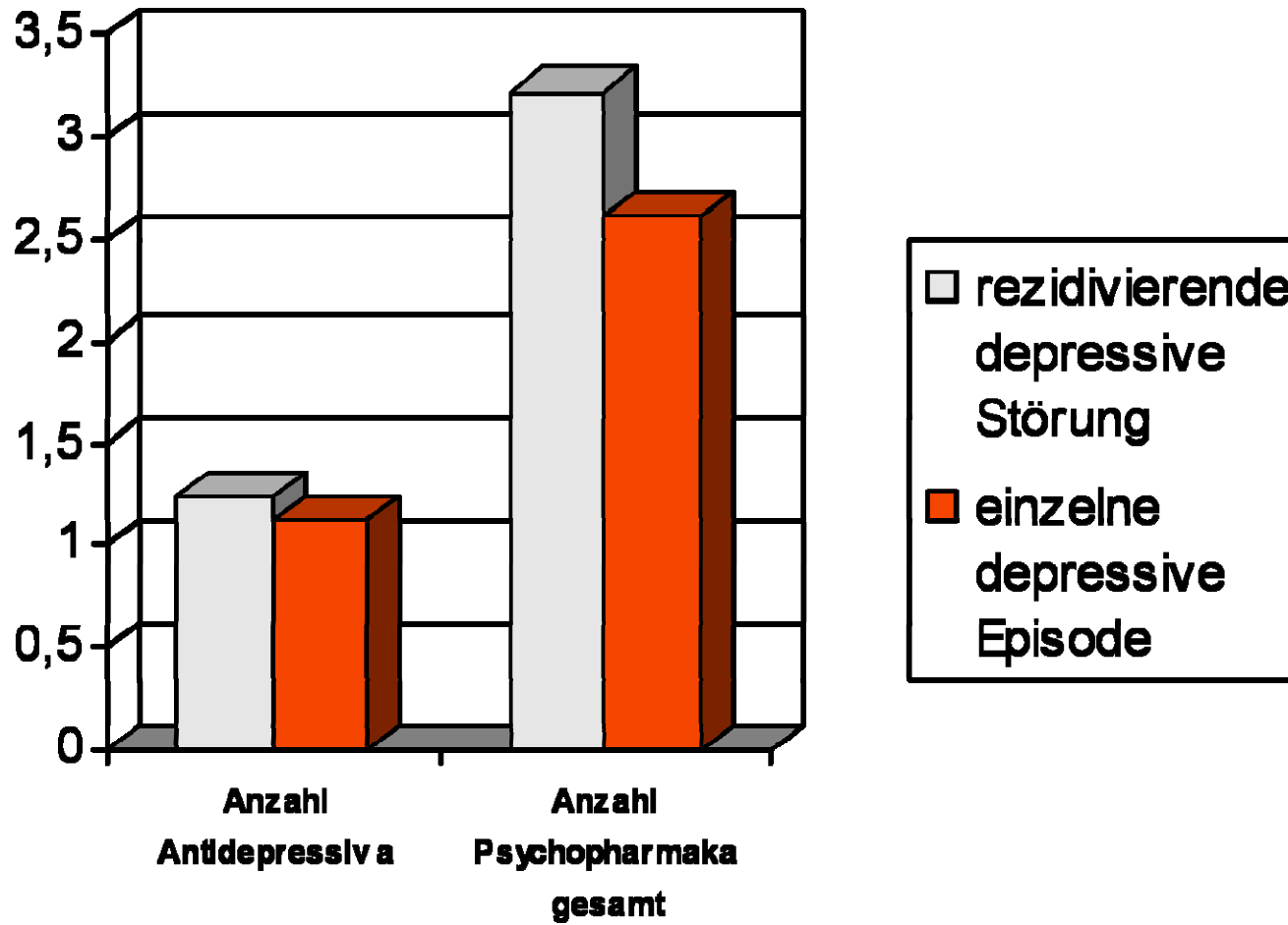


Die Wahrscheinlichkeit der Hypnotika-Einnahme ist bei CDES-Patienten signifikant größer als bei TAU (OR=3.949,  $p=.005$ ). Kein Unterschied zwischen SSTR und TAU (OR=1.870,  $p=.095$ ).



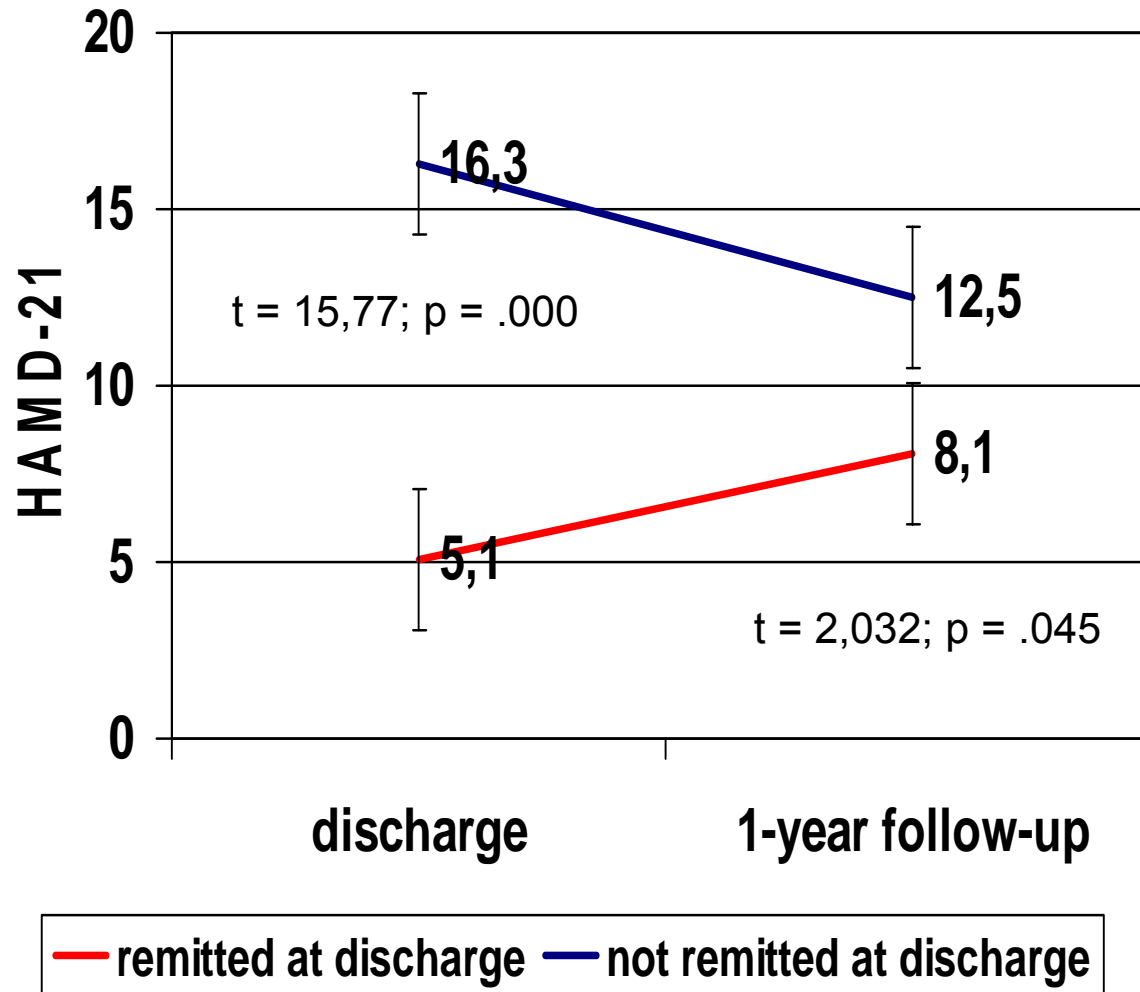
CDES und TAU haben eine höhere Wahrscheinlichkeit mit mindestens einem unterdosierten Antidepressivum behandelt zu werden als SSTR.







## Clinical outcome at follow-up predicts outcome after 1 year





## The German Algorithm Project -GAP2-

### SSTR treatment reduces inpatient treatment costs

	SSTR (n=74)	TAU (n=74)		TOTAL (n=148)
Average hospital costs	10 862.14 € (± 8 658.02)	15 247.97 € (± 12 520.29 )	t=-2,478 p=.014	13 055,06 € (± 10 950.48)
Remission rate	0,54	0,39		0,47
Costs/ remission	20 115.07 €	39 097.36 €		27 776.72 €

### Antidepressant Monotherapy

- amitriptyline (150 mg)
- sertraline (100 mg)
- reboxetine (8 mg)
- venlafaxine (225 mg)

### High dose Antidepressant Monotherapy

- amitriptyline (300 mg)
- sertraline (200 mg)
- reboxetine (12 mg)
- venlafaxine (375 mg)

### Lithium Augmentation

- serum levels (0,6-0,8 mmol/l)

### MAO-Inhibitor (tranylcypromine)

- medium: 30 mg
- high dose: 60 mg
- Ultra-high dose: 80 mg

### T3-Augmentation

- Tri-jode thyronine: 37,5 µg

### Electroconvulsive Therapy

3x / week

week	SSTR (I/1)	SSTR (I/2)	SSTR (I/3)	CDES (II)	TAU (III)		
0	Discontinuation period			COMPUTERIZED DOCUMENTATION- AND EXPERT SYSTEM Software-based pharmacotherapy	TREATMENT AS USUAL Free selection of treatment		
1	Antidepressant monotherapy						
2							
3							
4							
5	Lithium augmentation	High-dose antidepressant monotherapy	Change of drugs: antidepressant monotherapy				
6							
7							
8	Lithium monotherapy	Lithium augmentation	Lithium augmentation				
9							
10	MAO-inhibitor	Lithium monotherapy	Lithium monotherapy				
11							
12	High-dose MAO-inhibitor	MAO-inhibitor	MAO-inhibitor				
13							
14	ECT	alternative: Ultra-high-dose MAO-inhibitor	High-dose MAO-inhibitor			High-dose MAO-inhibitor	
15							
16	T3 augmentation	ECT	alternative: Ultra-high-dose MAO-inhibitor			ECT	alternative: Ultra-high-dose MAO-inhibitor
17							
18	T3 augmentation	ECT	T3 augmentation			T3 augmentation	
19							
20							

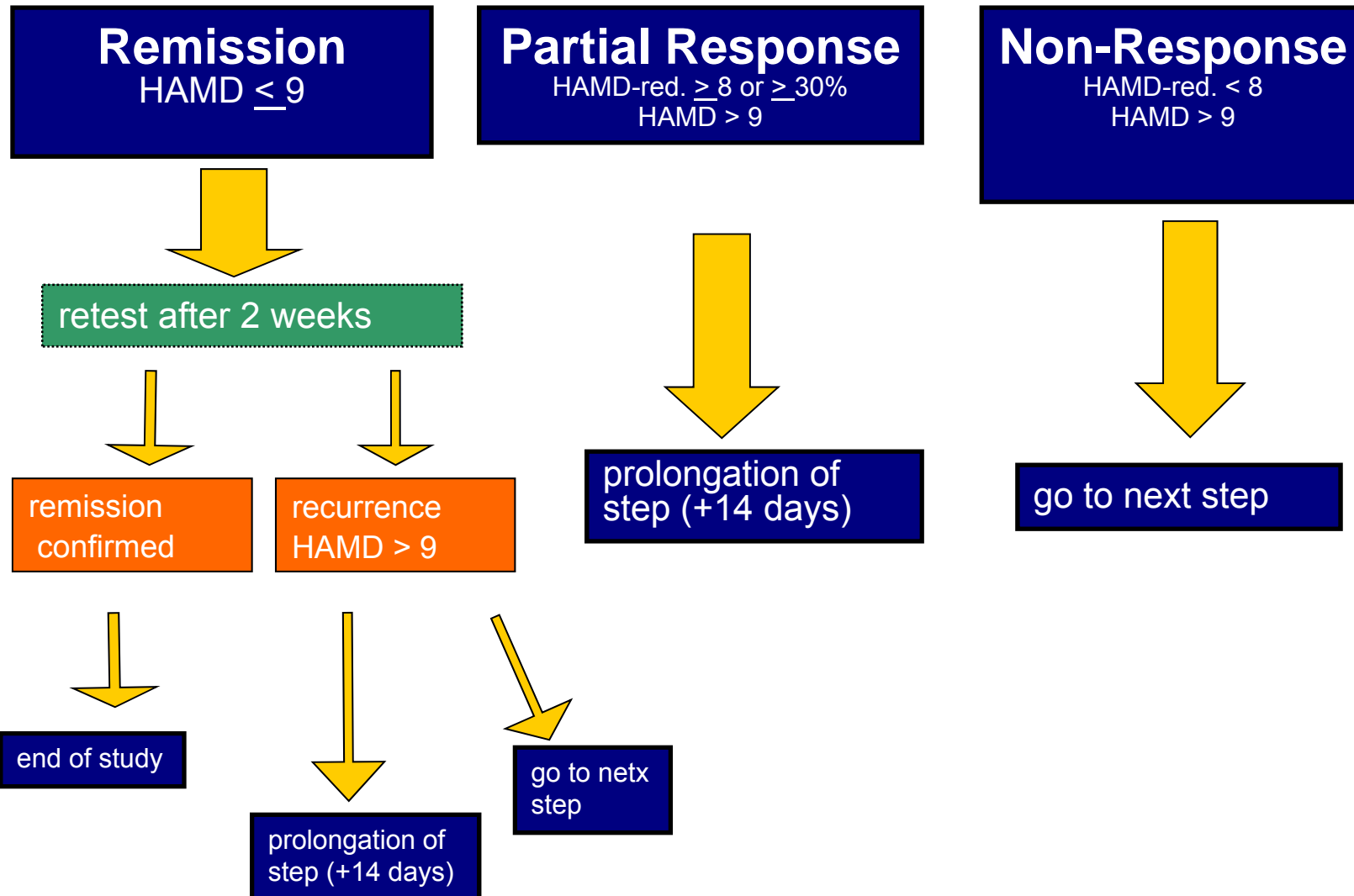
Gefördert vom



Bundesministerium  
für Bildung  
und Forschung



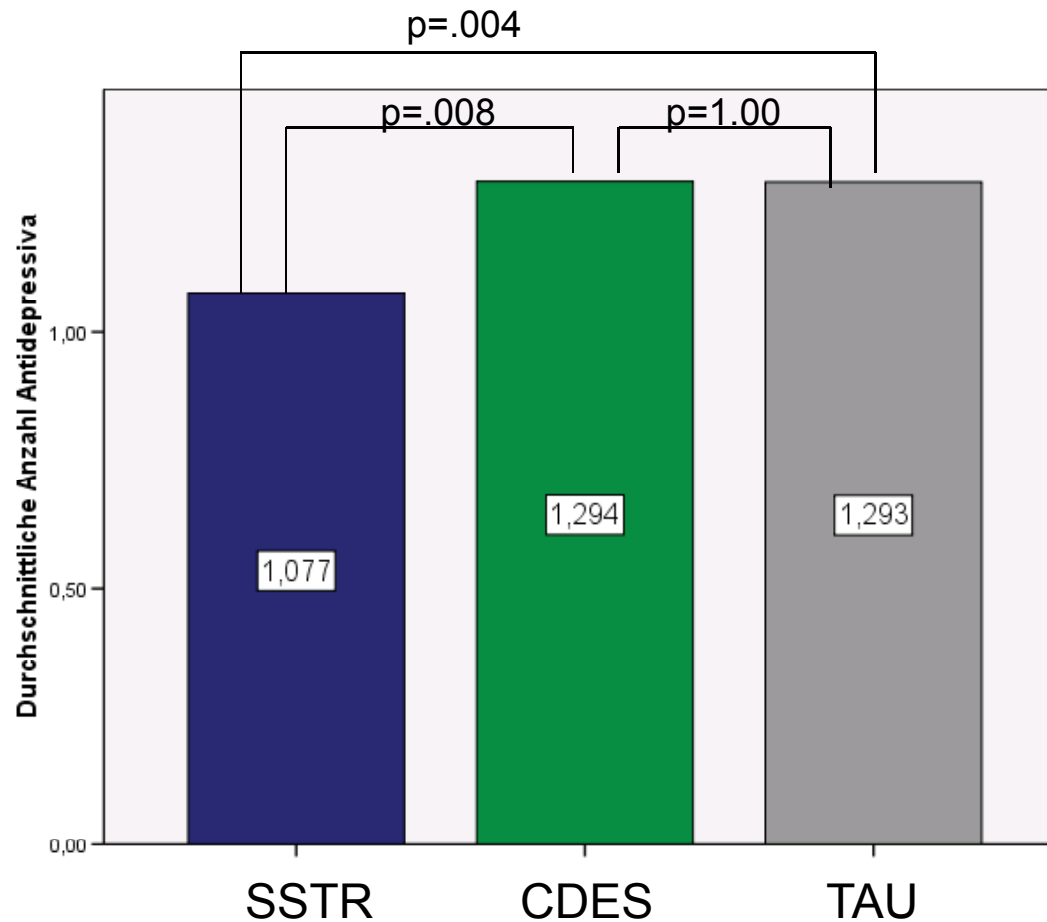
# Vorgehen bei Stufenplanbehandlung





## The German Algorithm Project, GAP 3

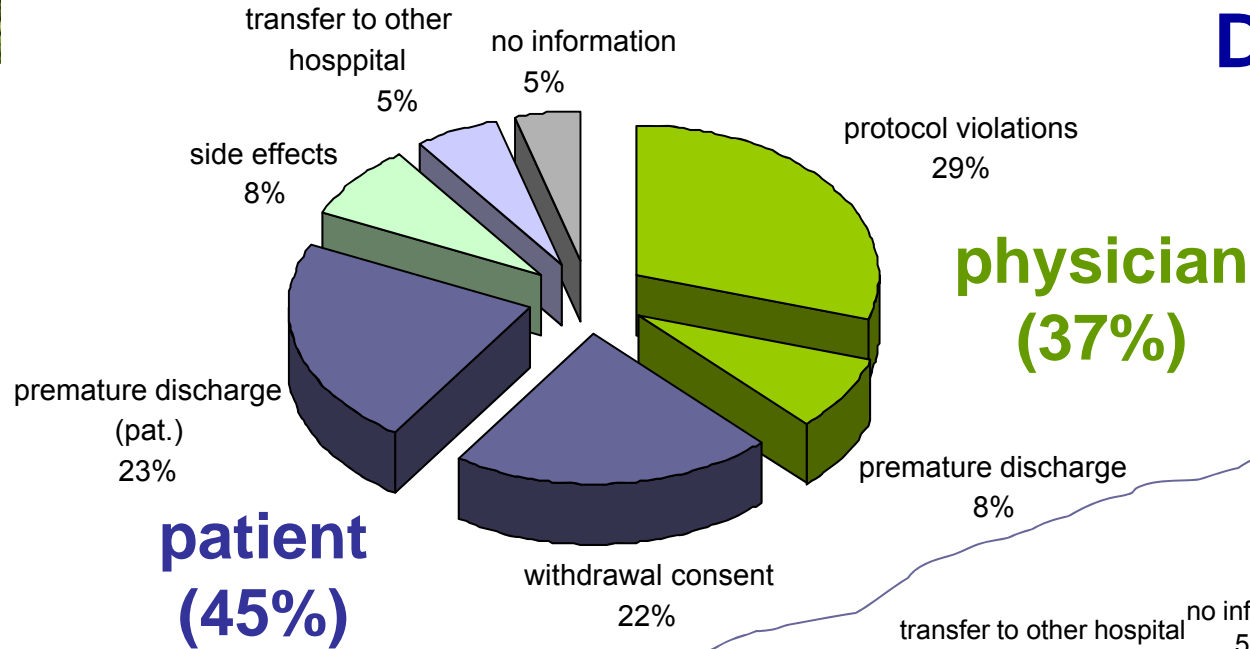
Anzahl Antidepressiva zum Erreichen von Remission unter Studienbedingungen



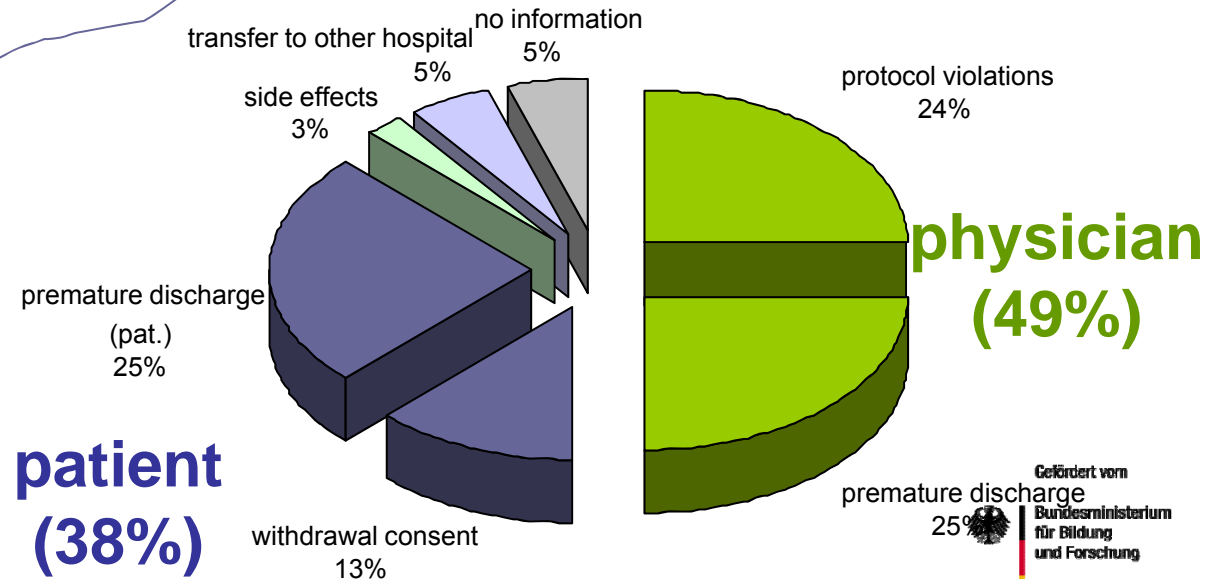
F=8,241; p=.000

# SSTR

## Dropout Reasons



# CDES



Chi<sup>2</sup> = 12.286; p = .092