Schwere Depressionen: Weniger Rückfälle unter Hypericum-Therapie

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KFN-Pressekonferenz

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Vergleichbarkeitsstudie WS® 5570 mit Paroxetin

Zielsetzung:

Untersuchung der Wirksamkeit von WS® 5570 im Vergleich zu Paroxetin bei Patienten mit mittelschwerer bis schwerer Depression

Hauptzielparameter: HAMD-Score

Vergleich der Responderraten und Verträglichkeit von WS® 5570 und Paroxetin.

(Szegedi et al., BMJ, 2005, Anghelescu et al., in Publikationsvorbereitung 2005)

Studiendesign Vergleichsstudie

Studiendesign:
- Randomisierte doppelblinde, doppel-dummy, Referenzkontrollierte Multicenter-Studie

Patienten:
- 251 Patienten mit akuter mittelschwerer bis schwerer Depression (Major Depression), Baseline HAMD (17 items) ≥ 22 Punkten

Studiendauer:
- 6 Wochen Akuttherapie
- 4 Monate Erhaltungstherapie

Dosierung:
- WS® 5570 (900 mg/Tag) oder Paroxetin(20mg/Tag)
- Erhöhung der Dosis auf 1800 mg/Tag WS® 5570 oder 40 mg/Tag Paroxetin bei anfänglichen Nichtrespondern (nach 2 Wochen)

Studiendesign

Einfachblind Placebo

Run-in-phase

(Tag -7/-3 bis Tag 0)

→

Randomisierte, Doppelblind-Phase, Akuttherapie

(6 Wochen)

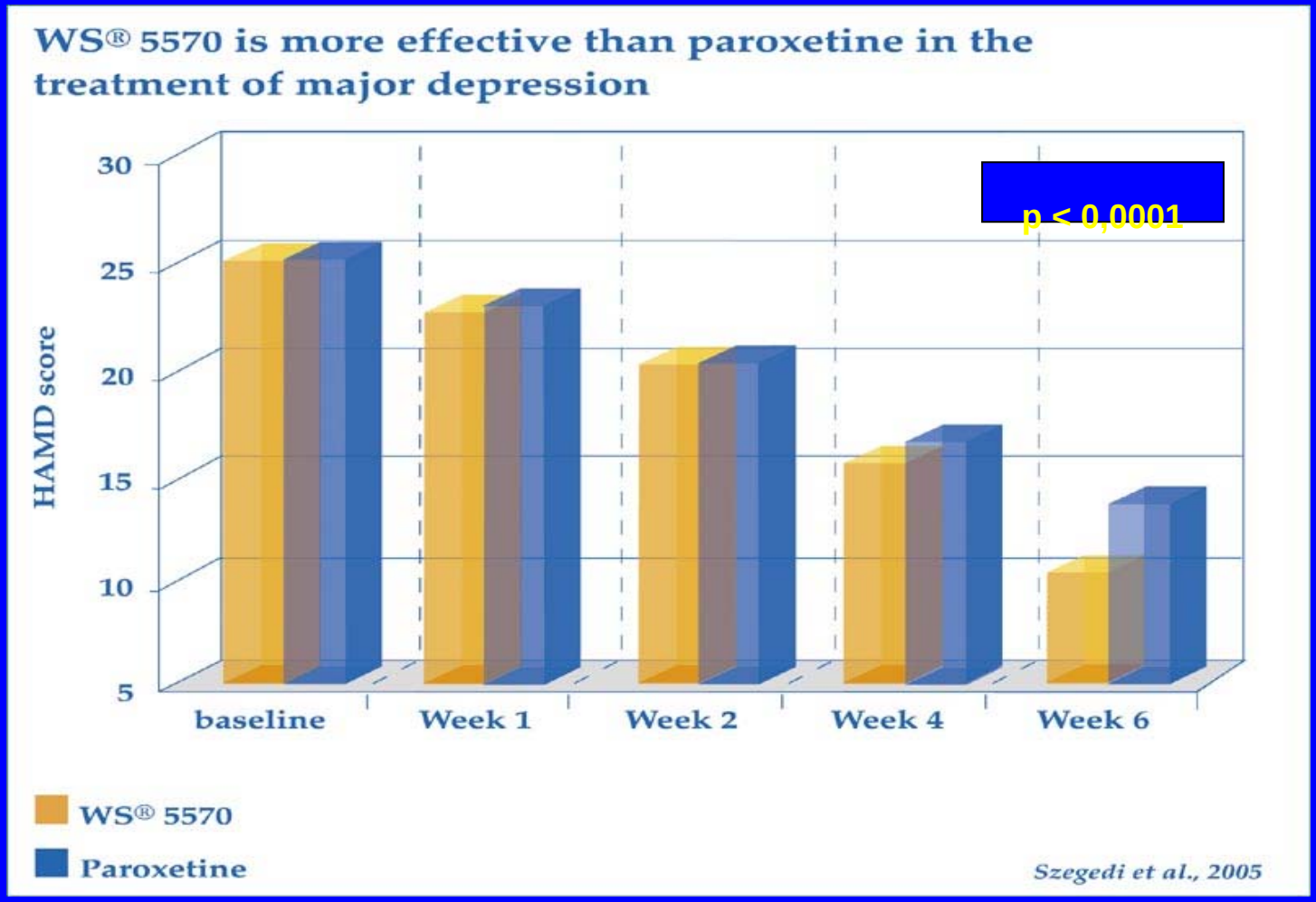
→

Therapie-responder werden in doppelblinde Erhaltungs-therapiephase aufgenommen

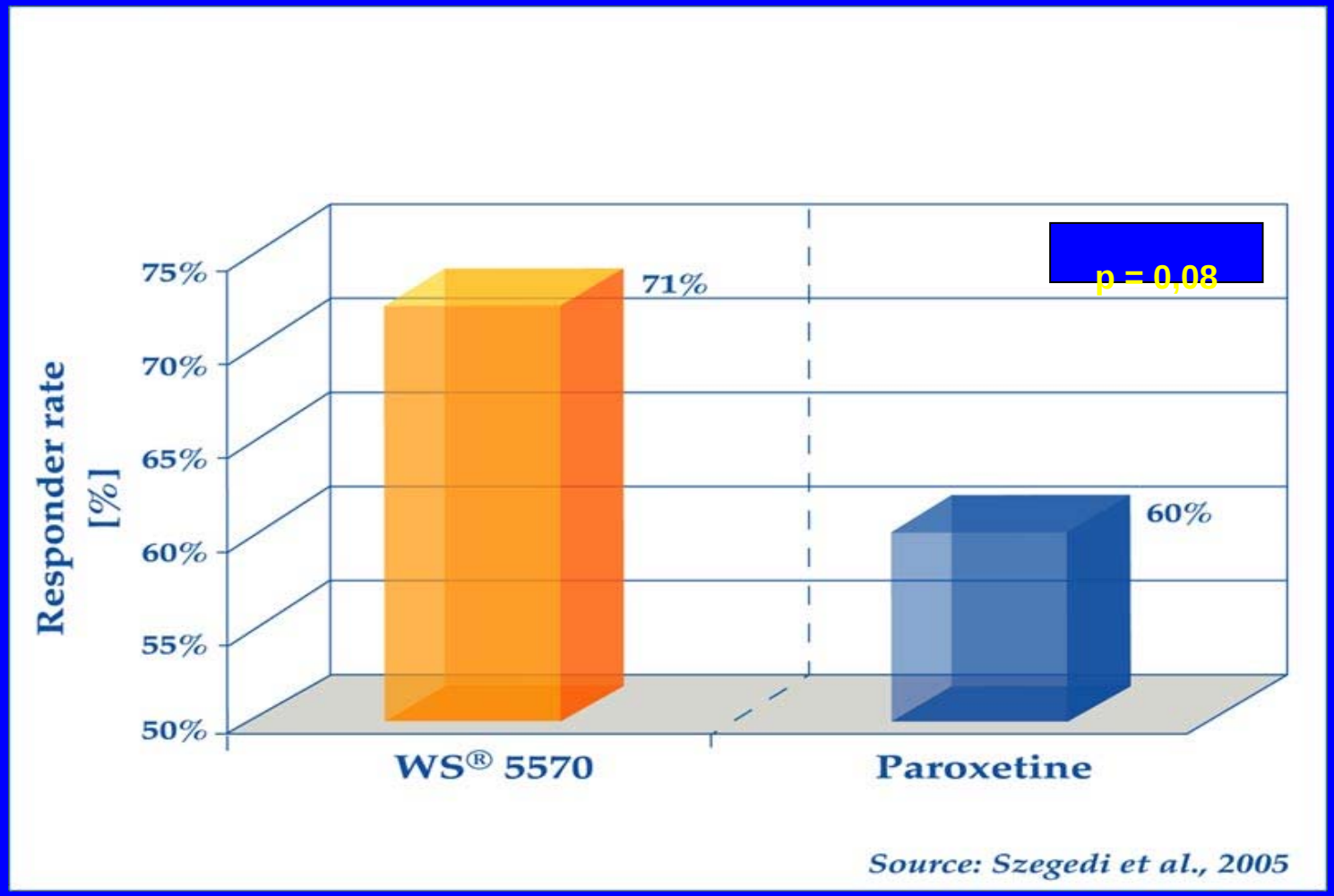
(4 Monate)

(Szegedi et al., BMJ, 2005, Anghelescu et al., in Publikationsvorbereitung 2005)

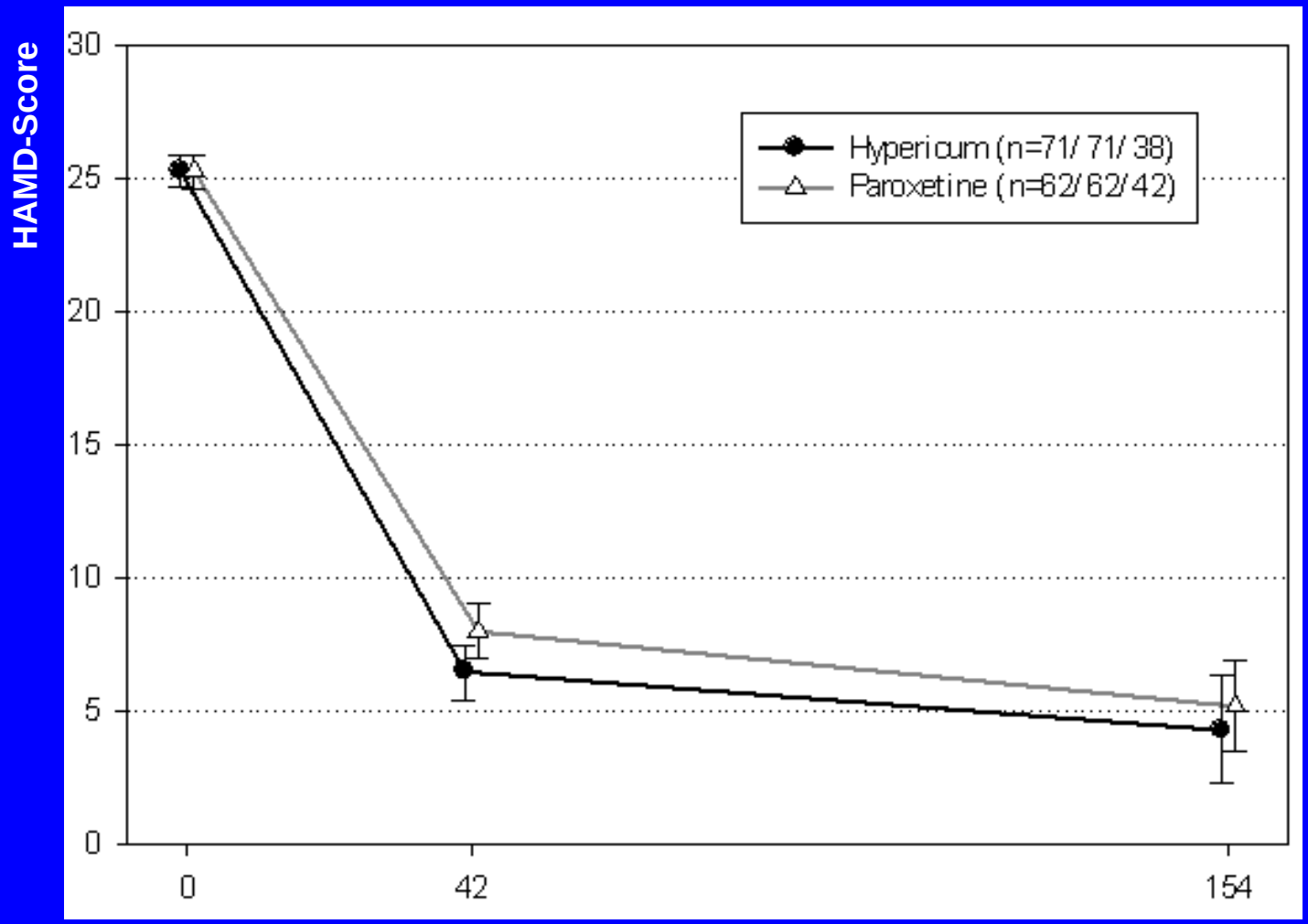
HAMD-Score Veränderungen nach Akutbehandlung



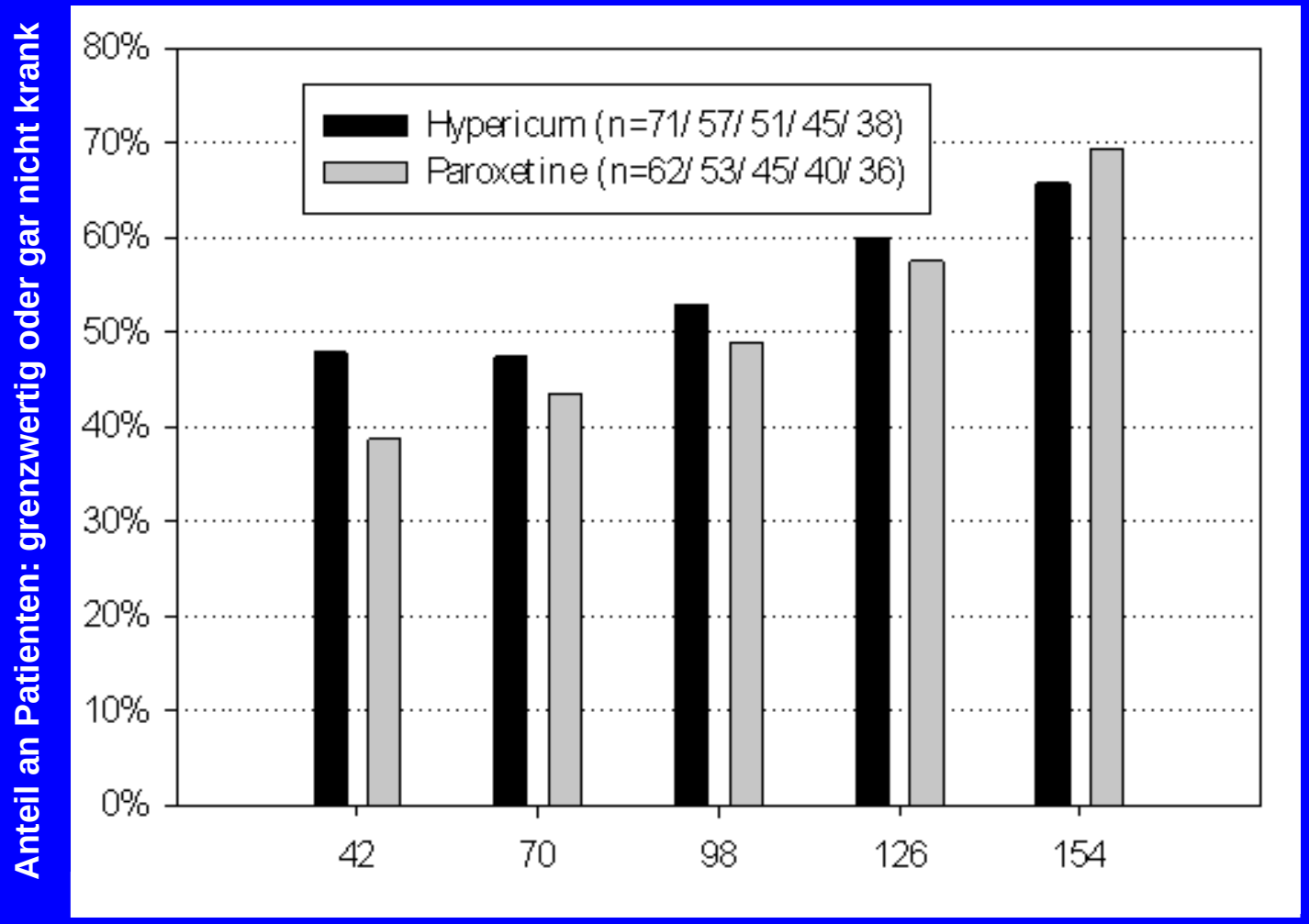
Responderraten nach Akutbehandlung



HAMD-Score Veränderungen in Akut- und Erhaltungsphase



CGI-Score Veränderungen (item 1) in Akut- und Erhaltungsphase



Ergebnisse

- Vergleichbare Wirksamkeit von Johanniskraut und Paroxetin, sowohl in der Akutbehandlung wie auch in der Erhaltungsphase durch HAMD-Score Veränderungen gezeigt
- Sekundäre Zielparameter (MADRS, CGI, BDI) zeigen vergleichbare Wirksamkeit von WS® 5570 zu Paroxetin
- Bessere Verträglichkeit von WS® 5570

Methodische Anforderungen an Studien zur Prävention und Relapseprophylaxe

- Adäquate Studienpopulation
- Unterscheidung „Relapse“ (Rückfall) und „Recurrence“ (Beginn neuer Krankheitsepisode)
- ausreichende Dauer der Erhaltungstherapie
- genaue Definition der Response und Remission in Rating Scales

S. Kasper, A. Dienel, M. Kieser, Int. J. Meth. Psych. Res. Vol. 13, 2004

Rationale für dieses Design:

Hypericumextrakt als interessante Alternative für eine Langzeit- und Rückfallprophylaxe

- ⇨ **Erfolgreiche Akutbehandlung**
- ⇨ **definierte Relapse-Erkennung**
- ⇨ **Unterscheidung Rückfall und Beginn einer neuen Episode**
- ⇨ **Prävention**

S. Kasper, A. Dienel, M. Kieser, Int. J. Meth. Psych. Res. Vol. 13, 2004

Neue Studie:Akutbehandlung der Depression - Erhaltungstherapie und Rückfallprophylaxe

Ziel der Studie:

Wirksamkeit und Verträglichkeit von Hypericumextrakt WS® 5570 während Langzeitbehandlung nach erfolgreicher Akuttherapie bei Patienten mit leichter bis mittelschwerer Depression.

Studiendesign:

Randomisierte, doppelblinde, placebo-kontrollierte Parallel-Gruppen-Multicenterstudie

S. Kasper, A. Dienel, M. Kieser, Int. J. Meth. Psych. Res. Vol. 13, 2004

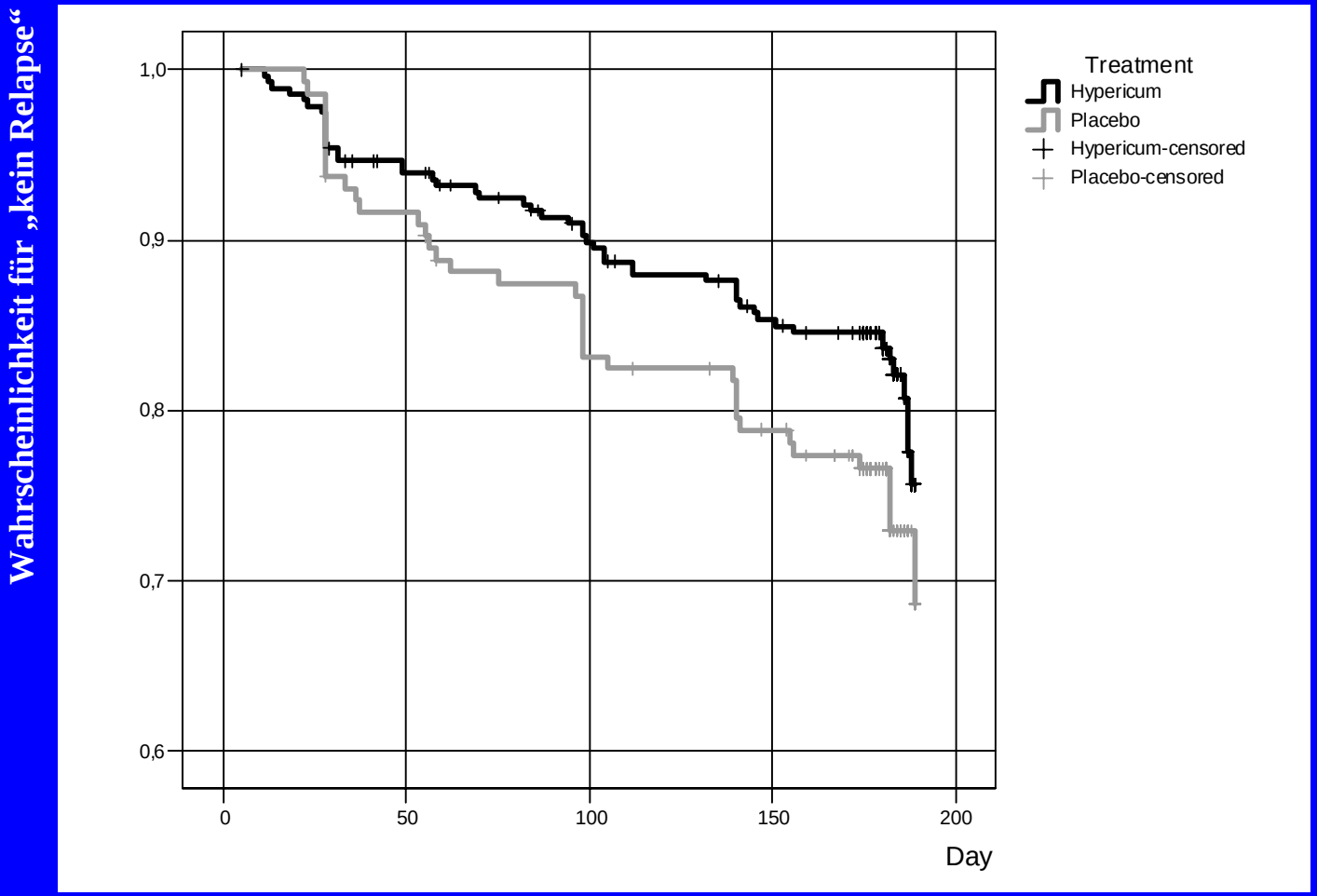
Anzahl der Relapse und Krankheits-veränderung unter Langzeittherapie

	WS® 5570 (n = 282)	Placebo (n = 144)	p-Wert*
Zeitintervall bis Auftreten eines Relapse	**177 ± 2,8 Tage**	**163 ± 4,4 Tage**	**p=0,041**
Relapse-Raten	**51 (18,1%)**	**37 (25,7%)**	**p=0,07**
CGI, item 1 Krankheitsausprägung	**208 (73.8%)**	**93 (64.6%)**	**p=0,02**
item 2 starke o. sehr starke Verbesserung	**247 (87.6%)**	**118 (81.9%)**	**p=0,02**

* zweiseitiger Test

Kasper et al., in Publikationsvorbereitung 2005

„Survival-Analyse“ bis Auftreten eines Relapse



Kasper et al., in Publikationsvorbereitung 2005

Zusammenfassung

- Auf die Akuttherapie (6 Wochen) 900 mg/Tag Hypericum extract WS® 5570 sprachen 81,1% von 703 Patienten an.
- Relapseraten waren 18,1% in der WS® 5570 Gruppe und 25,7% in Placebogruppe
- WS® 5570 zeigte relevante Therapie-Überlegenheit gegenüber Placebo während Erhaltungstherapie in der Relapseprophylaxe.
- Unerwünschte Ereignisse hatten eine Auftretensdichte von 0,005% für Verum und 0,006% für Placebo pro Behandlungstag

Schlußfolgerungen:

- Hypericumextrakt WS® 5570 ist für eine Langzeitprophylaxe der leichten bis mittelschweren Depression gut geeignet,
- denn:
  - Akutbehandlung mit WS® 5570 erfolgreich
  - Klare Ergebnisse zur Erhaltungstherapie und Rückfallprophylaxe mit WS® 5570
  - WS® 5570 mit geringer Nebenwirkungsrate, daher gute Compliance

Fazit:

- Hypericumextrakt WS® 5570 ist bei leichten bis zu schweren depressiven Störungen wirksam:
- - in der Therapie akuter depressiver Episoden.
- - in der Erhaltungstherapie und
- - Relapse-Prophylaxe.
- Wirksamkeit von WS® 5570 vergleichbar mit chemisch-synthetischen Antidepressiva.

Hypericum extract WS® 5570 in continuation treatment of recurrent depression

Authors

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AIMS AND OBJECTIVES

Unipolar major depression is a chronic disease that may require lifelong prophylaxis. Recovery from an acute episode is followed by 4–6 months of relapse prevention. After that, long-term maintenance treatment is administered to avoid recurrence. We investigated the efficacy of Hypericum extract WS® 5570[1] (drug extract ratio 3–7:1) in relapse prevention during continuation and long-term maintenance treatment following recovery from a recurrent episode of unipolar depression.

METHODS

- Design, treatments: prospective, multicenter, randomized, placebo controlled, double-blind trial. After 6 weeks of single-blind treatment with 3 × 300 mg/day WS® 5570 responders (score ≤2 on item 'Improvement' of the Clinical Global Impressions (CGI) + HAMD total score decrease ≥50% compared to baseline) entered 26 weeks of double-blind continuation treatment with 3 × 300 mg/day WS® 5570 or placebo.
- Subjects: 703 male and female adult outpatients included; 570 randomized after acute treatment; 426 (WS® 5570 282; placebo 144) evaluated for efficacy (full analysis set, FAS)
- Specific inclusion criteria:
  – recurrent, mild or moderate major depression (ICD-10 F33.0 or F33.1, and DSM-IV 296.3); ≥3 previous episodes within the last 5 years
  – Hamilton Rating Scale for Depression (HAMD; 17-item version) total score ≥20 points
- Primary outcome measure: time to relapse during continuation treatment (HAMD ≥16, clinical diagnosis of depression, or premature treatment termination for inefficacy)

	WS® 5570 (n=282)	Placebo (n=144)
Sex female male	 206 (73.0%) 76 (27.0%)	 109 (75.7%) 35 (24.3%)
Age [y]	47.5 (10.7) 48.0	47.7 (11.8) 49.0
HAMD (start of continuation phase)	8.6 (3.0) 9.0	8.7 (2.9) 9.0

Table 1
Demographic and clinical characteristics at baseline (FAS; absolute (relative) frequency, or mean (SD) and median).

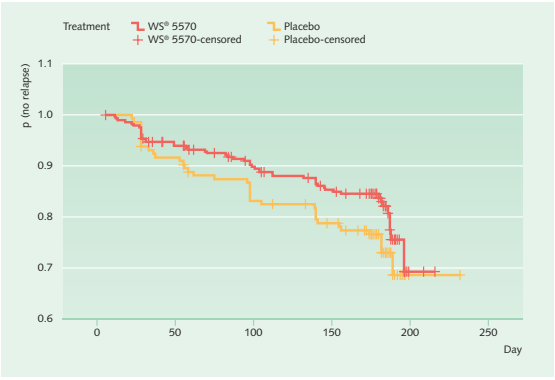

Figure 1
Time until relapse during continuation treatment (FAS).

RESULTS

- Relapse rates during continuation treatment: WS® 5570 18.1%, placebo 25.7%. Comparison of time to relapse (Figure 1) with log-rank test p=0.068 for FAS, p=0.062 for per protocol analysis.
- Secondary outcome measures of efficacy (HAMD, Montgomery-Åsberg Depression Rating Scale, Beck Depression Inventory, Clinical Global Impressions support more favourable outcomes in the WS® 5570 group (Table 2).
- Adverse events during continuation treatment: 0.005 per day of exposure for WS® 5570 and 0.006 for placebo.

DISCUSSION

Hypericum extract WS® 5570 showed a beneficial effect in preventing relapse during continuation treatment after recovery from acute depression. The herbal extract showed excellent tolerability in maintenance treatment, with over-all adverse event rates on the placebo level and no attributable serious events in a total of 703 patients exposed.

		WS® 5570 (n=282)	Placebo (n=144)	Difference WS® 5570 – placebo (with 95% confidence interval), two-sided p-value
Change in HAM-D	Week 32 – 6	–1.3 (5.7) –2.0	–0.1 (6.5) –2.0	1.18 (–0.02; 2.38) p=0.07*
Change in BDI	Week 32 – 6	–1.2 (2.3) –2.0 n=262	–0.7 (8.9) –2.0 n=132	0.49 (–0.16; 2.15) p=0.58*
CGI, item 1: not ill at all or borderline ill	Week 32	208 (73.8%)	93 (64.6%)	–0.09 (–0.19; 0.00) p=0.02**
CGI, item 2: much or very much improved	Week 32	247 (87.6%)	118 (81.9%)	–0.06 (–0.14; 0.01) p=0.02**

Table 2
Secondary efficacy measures (FAS; number (percent) unless stated otherwise).

* t-test; ** U-test for original ordinal data

[1] WS® is a registered trade mark of Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe

Hypericum extract WS® 5570 is at least equally effective and better tolerated than paroxetine in moderate to severe depression

Autoren

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aims and objectives

AIMS AND OBJECTIVES

While extracts from Hypericum perforatum (St. John's wort) are used widely and successfully in mild to moderate major depression, their efficacy in more severely depressed patients is debated. We investigated the antidepressant efficacy of Hypericum extract WS® 5570[1] (drug extract ratio 3–7:1) in patients with moderate to severe major depression by demonstrating at least non-inferiority to paroxetine, a potent selective serotonin reuptake inhibitor (SSRI).

	WS® 5570 (n=122)	Paroxetine (n=122)
Sex		
female	85 (69.7%)	83 (68.0%)
male	37 (30.3%)	39 (32.0%)
Age [y]	49.0 (11.0)	45.5 (11.5)
	51.5	48.0
HAMD	25.5 (2.7)	25.5 (2.9)
	25.0	25.0

Table 1
Demographic and clinical characteristics at baseline (FAS; absolute (relative) frequency, or mean (SD) and median).

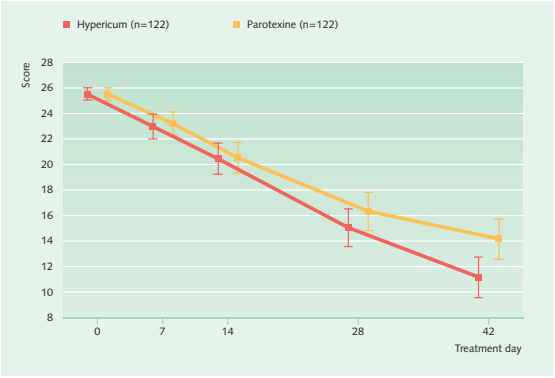

Figure 1
HAMD total score – change versus baseline (FAS, means and 95% confidence intervals, last observation carried forward).

methods

METHODS

- Design: prospective, multicenter, randomized, reference controlled, double-blind, double-dummy
- Subjects: 251 male and female adult out-patients (WS® 5570 n=125; paroxetine n=126; full analysis set (FAS): n=2 × 122)
- Specific inclusion criteria:
  – moderate or severe, single or recurrent episode of major depression (DSM-IV 296.22, 296.23, 296.32, 296.33)
  – Hamilton Rating Scale for Depression (HAMD; 17-item version) total score ≥22 points, ≥2 points for item 'depressive mood'
- Treatments: 900 mg/day WS® 5570 or 20 mg/day paroxetine for 6 weeks; after 2 weeks the dose in patients with insufficient initial response was increased to 1800 mg/day WS® 5570 or 40 mg/day paroxetine
- Primary outcome measure: HAMD total score change between baseline and end of treatment
- Non-inferiority margin Δ=2.5 points [1]

results

RESULTS

- HAMD total score change (points, mean ± SD; FAS):
  – Decrease by 14.4 ± 8.8 points (or 56.6% ± 34.3% of the baseline value) for WS® 5570 and by 11.4 ± 8.6 points (or 44.8% ± 33.5%) for paroxetine (Figure 1). Test for non-inferiority: p=0.102; test for superiority: p=0.0105 in favor of WS® 5570 (one-sided t-tests).
  – Responder rates (HAMD total score reduction ≥50%) WS® 5570 71%, paroxetine 60% (p=0.08); remission (HAMD endpoint total score <10) WS® 5570 50%, paroxetine 35% (p=0.02; one-sided χ^2-tests).
- Main efficacy results fully confirmed by per protocol analysis and all secondary outcome measures (Montgomery-Åsberg Depression Rating Scale, Beck Depression Inventory, Clinical Global Impressions;Table 2).
- Adverse events: 0.035 per day of exposure for WS® 5570 and 0.060 for paroxetine (ratio WS® 5570 / paroxetine 72% (95% confidence interval: 42% … 110%) advantage for WS® 5570).

discussion

DISCUSSION

Hypericum extract WS® 5570 is at least equally effective and better tolerated than paroxetine in the treatment of moderate to severe major depression.

References

[1] Montgomery SA. Clinically relevant effect sizes in depression. European Neuropsychopharmacology 1994;4:283–284.

[2] Szegedi A, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ 2005; 330:503–506.

		Hypericum (n=122)	Paroxetine (n=122)	Difference WS® 5570 – paroxetine (with 95% confidence interval), two-sided p-value
Change in MADRS (mean (SD), median)	Day 0 – 42	16.4 (10.7) 17.0	12.6 (10.6) 14.0	3.8 (1.1; 6.5) p=0.01*
Change in BDI (mean (SD), median)	Day 0 – 42	10.2 (10.3) 9.0 n=119	7.0 (9.3) 5.5 n=120	3.2 (0.7; 5.7) p=0.01*
CGI, item 1: improved by ≥2 categories	Day 42	71 (58%)	52 (43%)	16% (3%; 28%) p=0.02**
CGI, item 2: much or very much improved	Day 42	83 (68%)	70 (57%)	11% (–1%; 23%) p=0.09**
CGI, item 3: marked therapeutic effect	Day 42	49 (40%)	36 (30%)	11% (–1%; 23%) p=0.08**
Global efficacy self-rating: very good or good	Day 42	65 (53%)	55 (45%)	8% (–4%; 21%) p=0.20**

Table 2
Secondary efficacy measures (FAS; number (percent) unless stated otherwise).

* t-test; ** χ^2-test

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