

Tools for measuring clinical effectiveness in schizophrenia

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Why do schizophrenic patients refuse to take their drugs?

Van Putten, 1974

... although they suffer from a terrible and crippling
disease!

Maintenance antipsychotic therapy:

Is the cure worse than the disease?

Gardos and Cole, 1976

Change of treatment goals over the past 40 years

1960



- Reduction of (positive) psychotic symptoms

1980



- Long-term treatment
- Negative symptoms

1990



- Neuropsychological deficits
- Quality of life (QoL)/Subjective well-being (SW)

2000



- Early detection/delay of transition to psychosis

2005

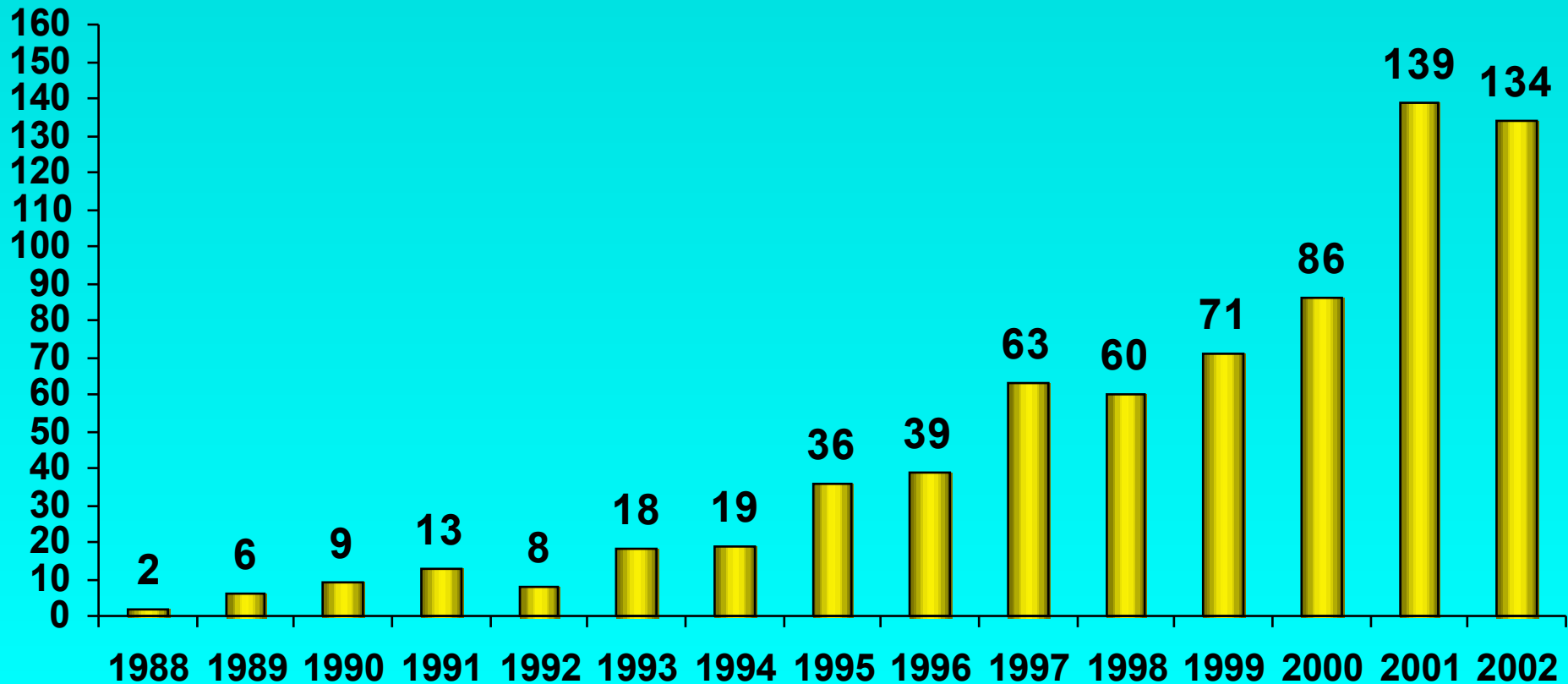
- Remission/recovery (functional outcome)

Scientific interest in patient's perspective and QoL under antipsychotic treatment

- Collins et al (1991) - measurement of therapeutic response in schizophrenia; literature search of clinical trials using key words 'drug' and 'psychosocial'
 - positive symptoms 98%
 - negative symptoms 19%
 - self-report or ratings of significant others 13%
- McKenna (1997) - measurement of QoL in schizophrenia; literature search
 - 500 papers
 - only 2 studies assessed the impact of antipsychotics on QoL (Meltzer et al 1990; Awad 1992)

Interest in Quality of Life in schizophrenia

Number of publications from 1988 to 2002
(Medline, Pub-Med. Recherche, 2003)



Main reasons for neglecting QoL and SW in schizophrenia¹

- Lack of agreement on definition, on essential components of QoL or SW and on rating scales
- Self-rated judgment of QoL or SW is often disqualified as unreliable
- Before availability of atypicals, only limited ways to consider patient`s complaints
- Since 1996 official outcome criteria in psychiatry

Quality of life measurement in schizophrenia

- Numerous scales are available (generic versus disease-specific, self- versus expert-rated). Comparative data on variables such as sensitivity to treatment effects, predictive power regarding compliance or chance of remission are very limited.
- Disease-specific scales seem to be more sensitive than generic scales, self-rated scales are less time consuming and might be more useful than interview-based scales.
- Quality Of Life scale (Heinrichs et al., 1984) is most widely used. 21-item semi-structured interview to assess QOL in relation to deficit symptoms and impaired functioning. Total score and 4 subscores, 45 minutes.

Subjective effects of antipsychotics

- Many schizophrenic patients treated with typical antipsychotics report not only motor effects, but also emotional and affective restrictions – ‘I feel like a zombie’. These patients benefit particularly from atypicals.
- Complaints are well known (pharmacogenic depression, akinetic depression, pharmacogenic anhedonia, neuroleptic-induced deficit syndrome), but barely investigated. They are often too subtle to be detected by objective examination and the common rating scales.
- Symptoms are often difficult to differentiate from negative symptoms of schizophrenia.

Three personal experiences on the relevance of subjective effects

- Clozapine (1975-1985). Many patients report that under clozapine they "feel better" than under previous neuroleptic drugs, objectively barely noticeable
- Clinical Trial of Partial Dopamine Agonist. In the open trial, the antipsychotic was very well tolerated. Most patients regretted discontinuation when study was completed. In the controlled trial, no difference to haloperidol. However, in comparison to previous neuroleptics, patients favoured significantly the experimental drug.
- Dysphoric, anhedonic experience, induced by 2-5 mg haloperidol

Patients' perceptions of efficacy differs from clinicians' assessment

- In a six-months open trial, patients receiving atypical antipsychotics reported fewer side effects, better subjective efficiency, better QoL and less neuroleptic dysphoria than patients treated with classical antipsychotics ($p < .05$)
- However: These perceived benefits were not reflected in the clinician-rated (objective) measures of psychosocial functioning and QoL

Subjective well-being under neuroleptics (SWN)

- The self-report of 20 items (10 positive, 10 negative, Lickert scale) shows sufficient internal consistency (Cronbach's α .92) and good construct validity. Most patients do not need more than 5-10 minutes to fill it out.
- There are 5 subscores (emotional regulation, self-control, social integration, mental and physical functioning).
- SWN data indicate relevance for compliance and for the chance to reach remission.
- Correlations to Heinrichs QLS during short- and long-term treatment $r = .4-.7$.

Self-report of well-being by schizophrenic patients

- All statements refer to the past 7 days.
- Total score, 5 subscores (e.g. physical functioning)

	Not at all	A little	Somewhat	Noticeable	Much	Very much
My body is a burden to me						
I feel very comfortable with my body						
I feel weak and exhausted						
My body feels familiar						

Are schizophrenic patients able to self-rate?

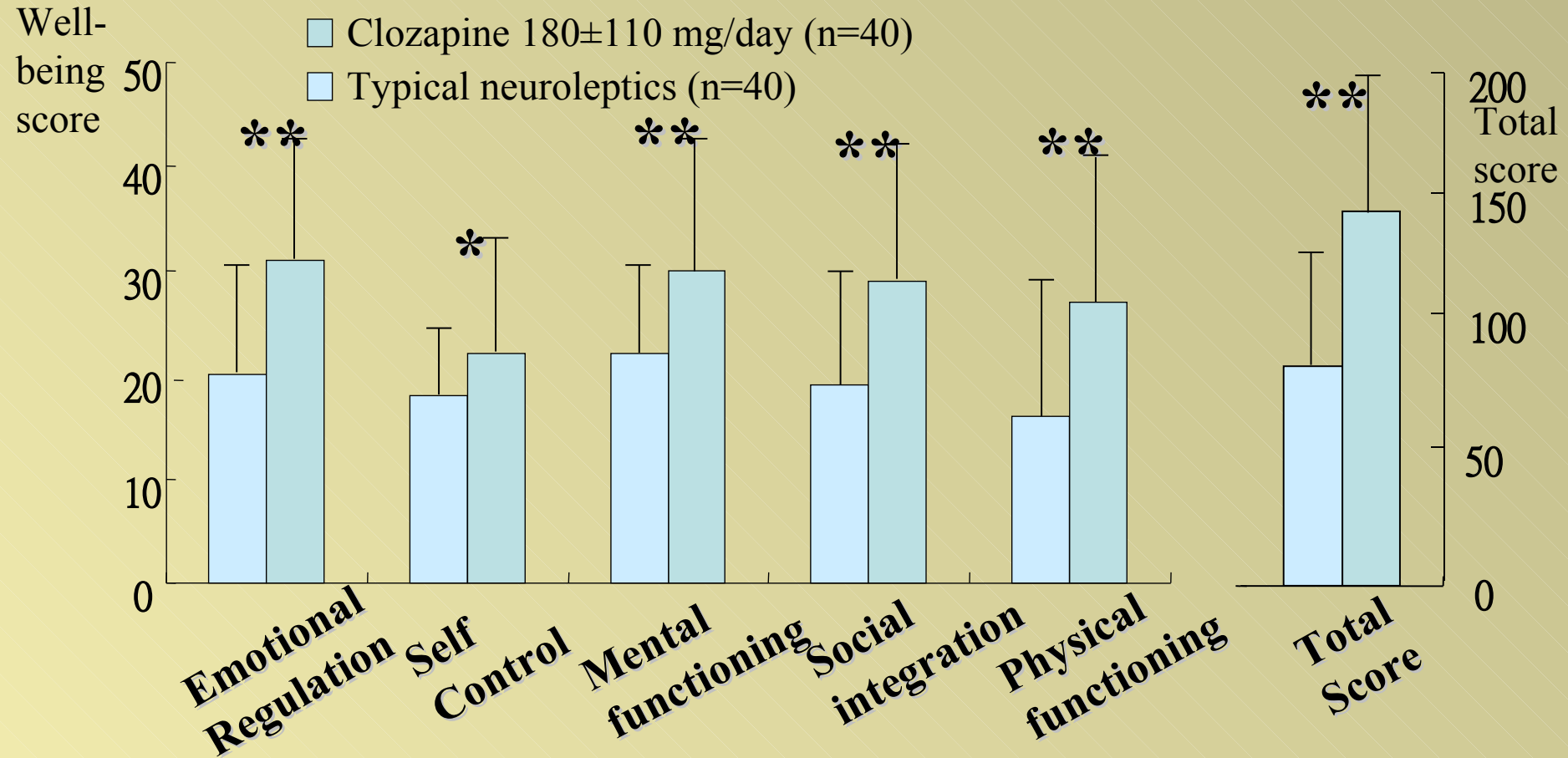
- 63%–95% of schizophrenic patients mostly in remission were able to self rate
 - their affective state (Craig and Van Natton, 1971; Weissmann, 1976; Brown et al, 1979; Maurer and Dittrich, 1979; Hogan et al, 1983; Bandelow et al, 1990)
 - or their quality of life (Naber et al, 1995; Voruganti et al, 1998; Khatri et al., 2001; de Haan et al., 2002; Voruganti et al., 2002; Liraud et al., 2004)
 - in a reliable manner.

Psychometric Properties of the Subjective Well-Being Under Neuroleptics Scale

L. de Haan et al, Psychopharmacology, 2002

“Almost all patients were capable of reproducing their subjective experience in a consistent way. The SWN may be used in evaluating differential effects of anti-psychotics and dose on subjective well-being”

Self-rated well-being with clozapine

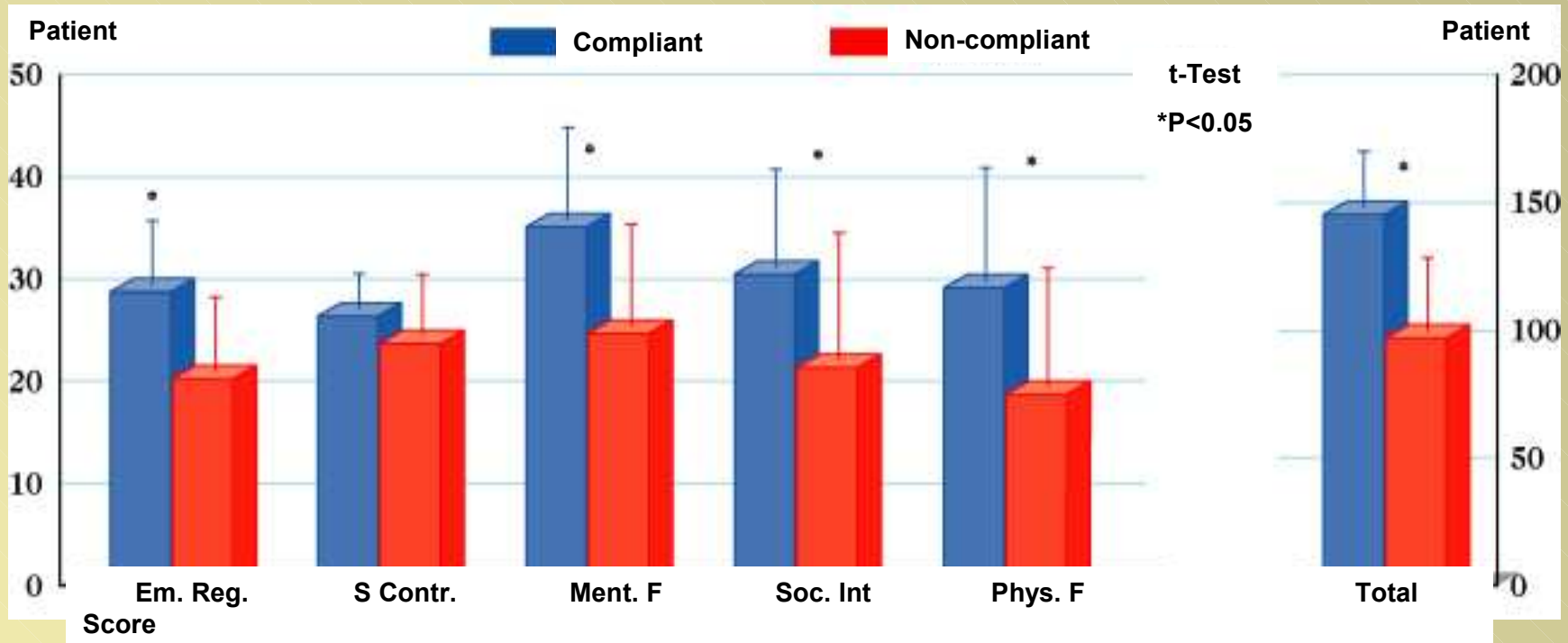


* $p < 0.05$; $p < 0.02$ (t-test); 195±110 mg/day chlorpromazine equivalents (haloperidol or flupenthixol)

Relationships to compliance

48 schizophrenic patients completed self-rating shortly before dismissal and 4–6 months later. Moreover, the private psychiatrist was asked regarding compliance.

Already at dismissal, the 14 patients who were non-compliant 4–6 months later, rated their well-being significantly worse than the 34 compliant patients. Psychiatrist's ratings (PANSS, BPRS) did not yet differ.



Is self-rating a valid tool in the early recognition of non-compliant patients?

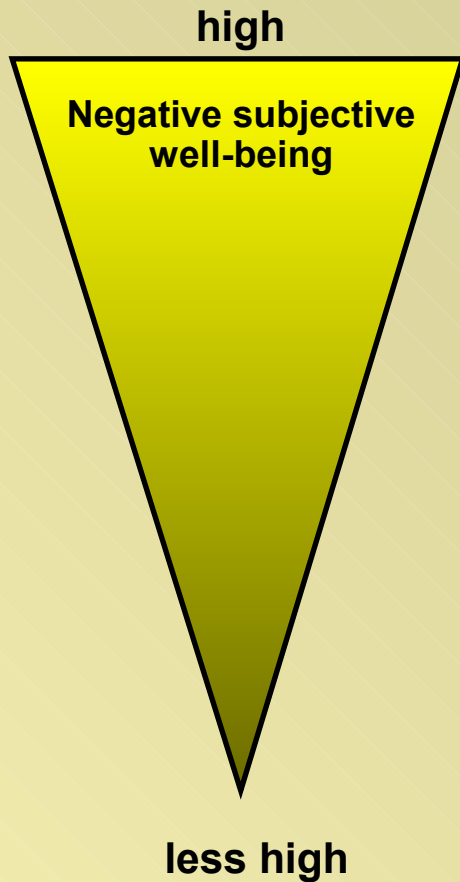
Therapeutic consequences: information, depot-injection, change of drug or dosage, out-patient treatment more frequent.

Improvements of Psychopathology and Subjective Well-Being under Atypical Neuroleptics are not strongly related

- Relationship between individual changes of SWN and PANSS in 97 schizophrenic in-patients treated with olanzapine (n=36), risperidone (n=28) or clozapine (n=36) for 30-58 days
- $r=-0.29$, $p<0.006$

Naber D, et al. *Schizophr Res.* 2001;50(1-2):79-88.

Relationships between SW/QoL and expert-rated psychopathology



Depressive Symptoms

Carpiniello et al. (1997) $r = -.3$ bis $-.4$ (< 0.01)
 Dickerson et al. (1998) $r = -.45$ (< 0.01)
 Franz et al. (1997) $r = -.35$ (< 0.01)
 Karow et al. (in press) $r = -.4$ (< 0.01)

Negative Symptoms

Meltzer et al. (1990) $r = -.3$ bis $-.4$ (< 0.01)
 Browne et al. (1990) $r = -.69$ (< 0.01)
 Naber et al. (1994) $r = -.3$ bis $-.4$ (< 0.01)
 Gervin et al. (1999) $r = -.5$ (< 0.001)
 Bow-Thomas et al. (1999) $r = -.45$ ($p < 0.05$)
 Naber et al. (2001) $r = -.4$ (< 0.01)

Positive Symptoms

Meltzer et al. (1990) $r = -.2$ bis $-.3$ (ns)
 Browne et al. (1990) $r = -.21$ (ns)
 Naber et al. (1994) $r = .1$ bis $-.2$ (ns)
 Naber et al. (2001) $r = -.1$ (ns)

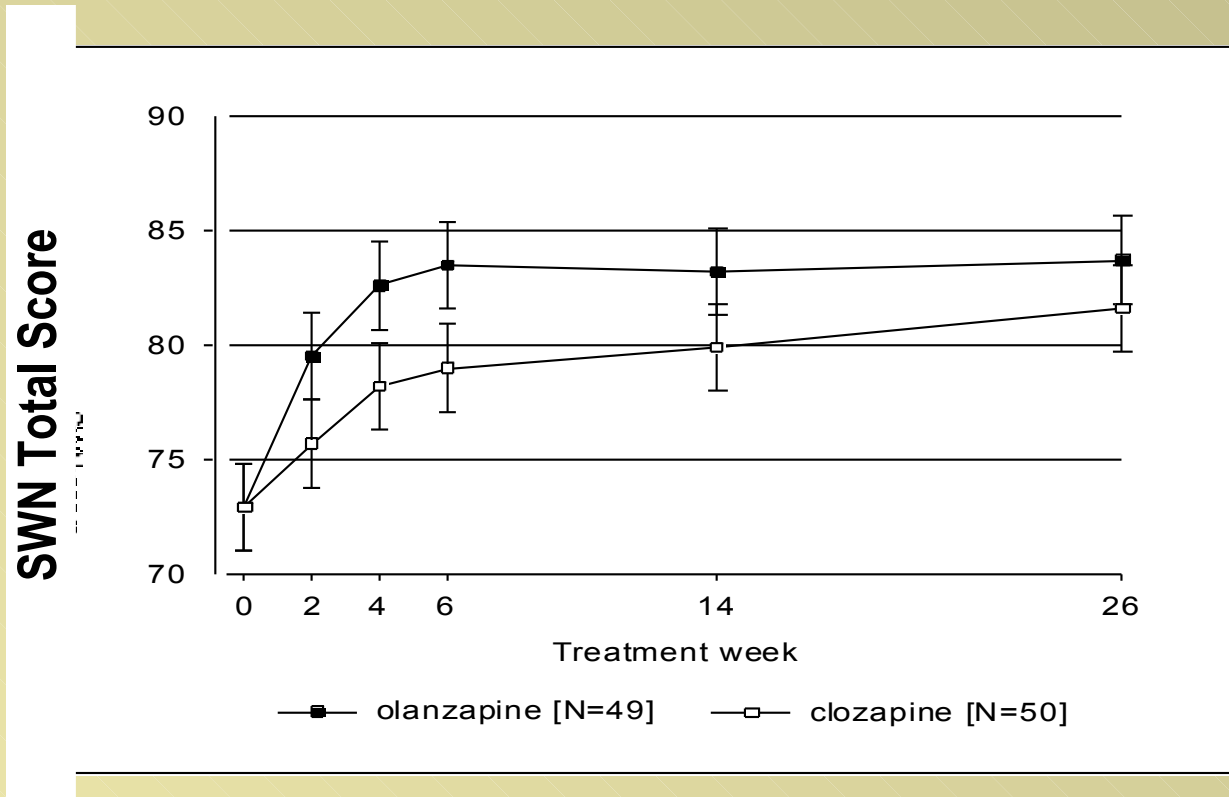
1. Lambert M et al., Pharmacopsychiatry 2003; 36 Suppl 3:181-90.

Relationship between SWN and Psychopathology (Karow et al., 2005)

PANSS syndromes	Baseline (n=84)	Discharge 42±28 days (n=84)	Follow-up 6 months (n=39)
Hostile Excitement	-.01	-.37*	-.15
Negative Syndr.	-.34*	-.22	-.43*
Cognitive Syndr.	-.12	-.26	-.10
Positive Syndr.	-.13	-.33*	-.09
Depression	-.30*	-.38*	-.67*

Correlation Coefficient *p<.01

Double-blind Comparison of Olanzapine and Clozapine



Δ SWN - Δ PANSS, $r = -.45$, $p = .003$

Animal data on affective changes with (typical) antipsychotics

- Extensive animal data indicate the importance of mesocortical dopamine (mostly D2) systems in mediating reward behaviour
- Several animal studies have demonstrated that typical antipsychotics strongly and negatively affect reward system(s) in a variety of models
- Less or none inhibition of reward systems by atypical antipsychotics ?

Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D₂ receptors: a PET study in schizophrenia

(Mizrahi et al., 2007)

- In 12 patients, treated with 1 mg RIS (n=2), 4 mg RIS (n=3), 2,5 mg OLA (n=3) or 15 mg OLA (n=4) striatal and temporal dopamin-D₂-occupancy (50-91%, 4-95%) as well as PANSS, SWN and motor symptoms were assessed.
- SWN and PANSS were not significantly correlated ($r=0,11$, $p=0,78$) but SWN with Simpson-Angus Score ($r=-0,71$, $p=0,047$).
- SWN and D2-occupancy were significantly correlated in the striatum ($r=-0,66$, $p=0,01$) as well as in the temporal lobe ($r=-0,76$, $p=0,003$).

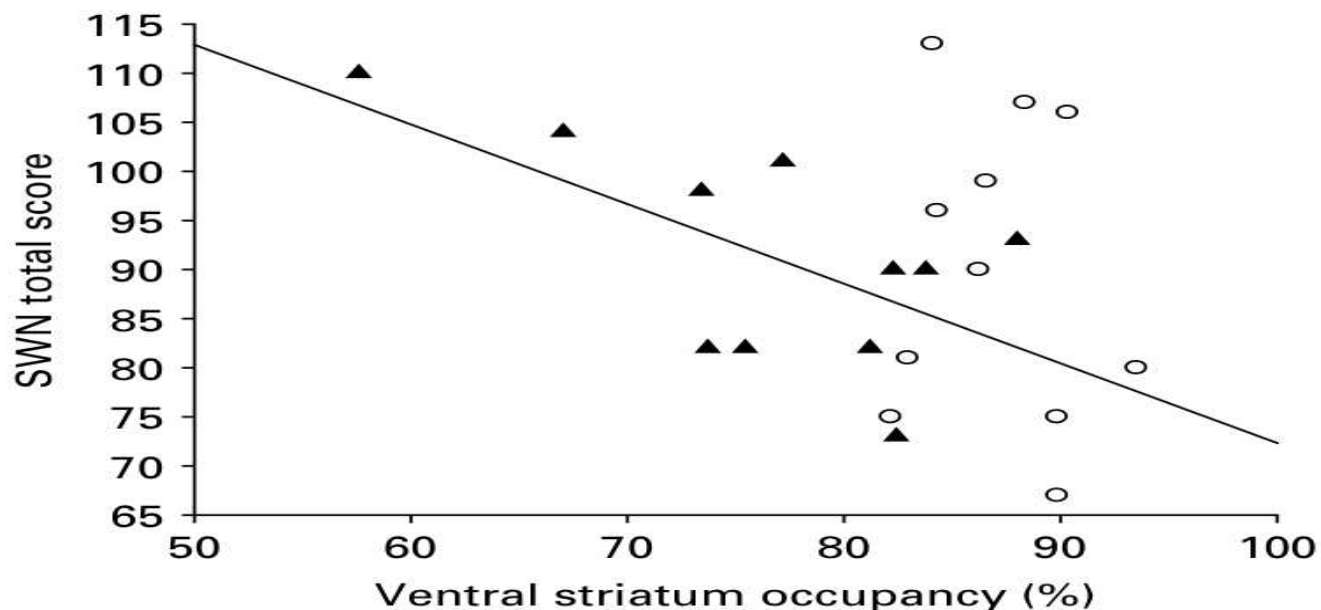
**Relationships between SWN and Dopamin D2 Receptor Occupancy:
Striatal $r = -.66$, $p = .01$, temporal, $r = -.76$, $p = .003$ (Mizrahi et al., 2007)**

Zur Anzeige wird der QuickTime™
Dekompressor „TIFF (LZW)“
benötigt.

The relationship between SWN and dopamine D2 receptors in patients treated with a dopamine partial agonist and full antagonist antipsychotics (Mizrahi et al. 2009)

- 22 patients with a diagnosis of schizophrenia participated, 11 were switched to aripiprazole (18 ± 8 mg), and 11 patients were continued to be treated either with risperidone (1.9 ± 0.9 mg) or olanzapine (17.9 ± 7.8 mg).
- A PET scan was carried out two to three weeks after the beginning of aripiprazole treatment. No significant relationship between SWN and striatal D2 occupancy in aripiprazole patients ($r = -0.43$, $p = 0.18$), but in patients treated with antagonist antipsychotics ($r = -0.63$, $p = 0.04$).

The relationship between SWN and dopamine D2 receptors in patients treated with a dopamine partial agonist and full antagonist antipsychotics (Mizrahi et al. 2009)



- Association between SWN total score and D2 occupancy in partial agonist-treated (aripiprazole; ○) vs. full antagonist antipsychotic-treated (risperidone or olanzapine; ▲) patients.
- Aripiprazole $r = -0.43$, $p = 0.18$
- Full antagonists $r = -0.63$, $p = 0.04$

Impact of Side Effects on SWN

- Under treatment with typical AP, EPS are most disturbing
- Under atypical AP: sexual SE, weight gain and sedation
- High interindividual variation!

SNW and Gait Performance

(Putzhammer et al., 2005)

- 25 schizophrenic patients, treated with typical antipsychotics (TYP), 25 with atypicals (ATYP), and 16 drug-naive were investigated by an ultrasonic gait analysis.
- Stride length was found to be significantly ($p < .01$) correlated with SWN score in TYP, but not in ATYP.
- Under TYP, SWN depends on motor side effects, under ATYP and drug-naive, mostly on general psychopathology ($p < .01$) and negative symptoms ($p < .05$).

European SOHO Study

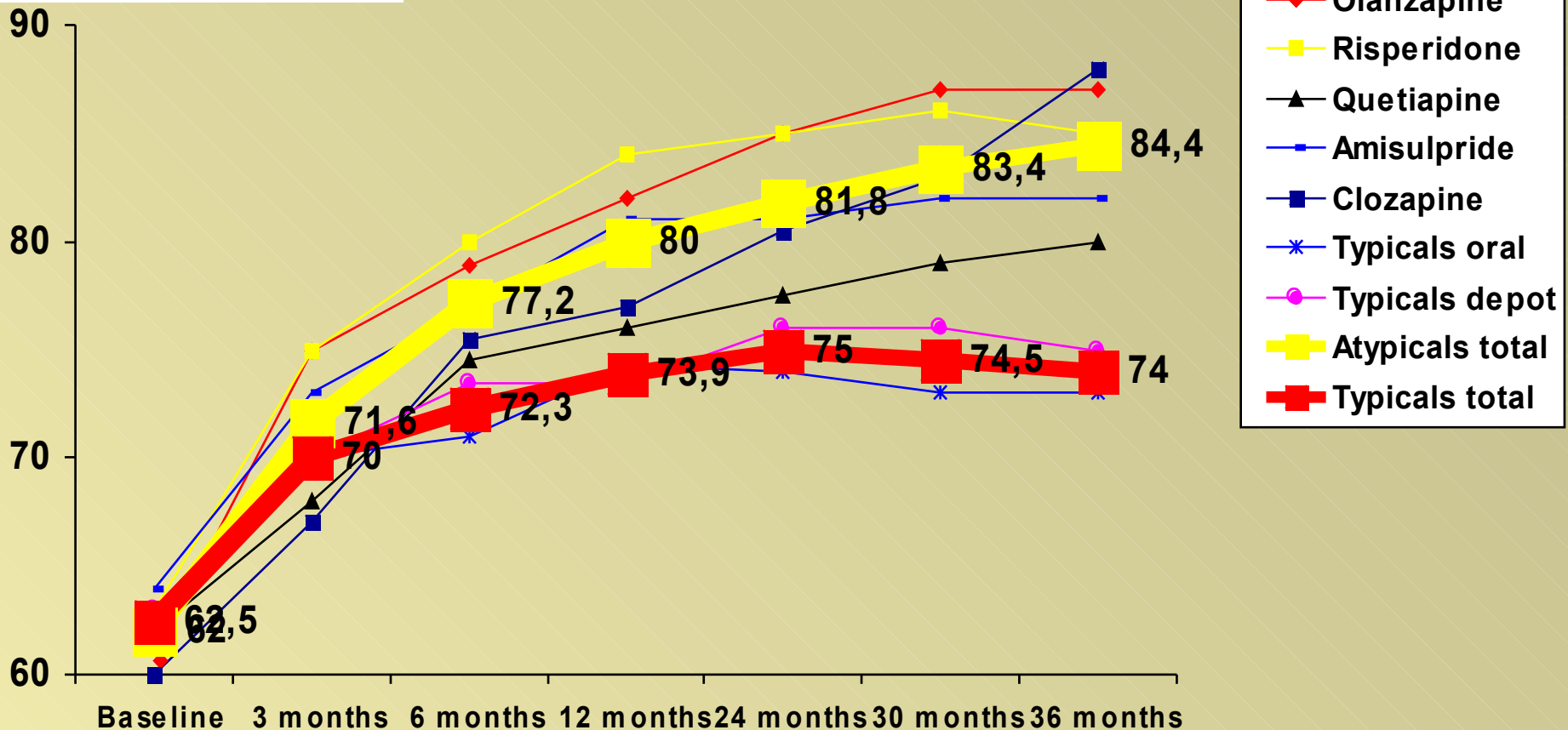
- Comparison at baseline, 3, 6 and 12 months of patients initiating / changing to / adding treatment with olanzapine, risperidone, quetiapine, amisulpride, clozapine, oral typicals (PO Typical), depot typicals
- Treatment cohorts were defined based on the drug newly initiated or added at baseline documentation
- Prospective non-interventional/observational study over 3 years, all patient care is at the discretion of the participating psychiatrists
- 10,972 patients enrolled across 10 countries, 3,499 in Germany, where the SWN was used



Subjective well-being: 36-month results of the SOHO study (N=2960)

SOHO

Schizophrenia Outpatient Health Outcomes



Lambert et al. Schizophr Res; in preparation.

Definition of remission in the SOHO study ¹



2960 patients with schizophrenia for more than 2 years ¹

Remission was defined as at least 6 months of :

- **Symptomatic remission:**
 - **CGI-Severity total score ≤ 3 ; CGI-Severity positive and cognitive subscore ≤ 3 ; CGI-Severity negative subscore ≤ 4**
- **Functional remission:**
 - **Work: full or part time, student or housekeeping**
 - **Ability to lead an independent life (lives alone, with partner or friends)**
 - **social contacts (≥ 2 /week)**
- **Remission of subjective quality of life:**
 - **Subjective well-being (SWN-K) ≥ 80 points (range 20-120 points)**

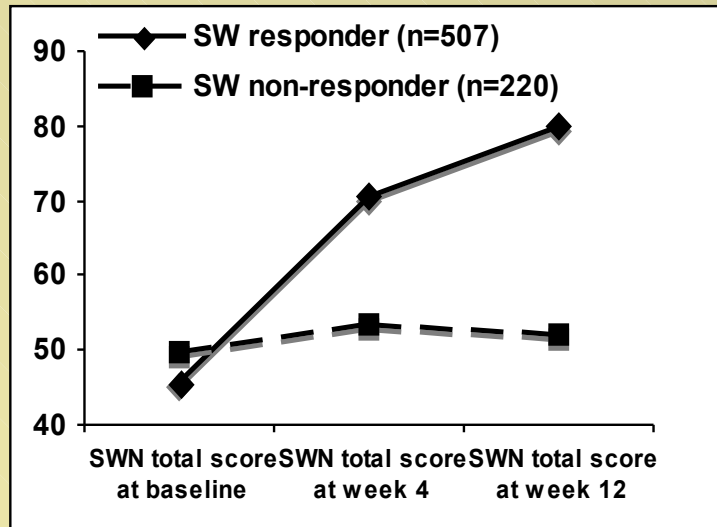
Combinations of Remission Definitions

at 24 Months¹

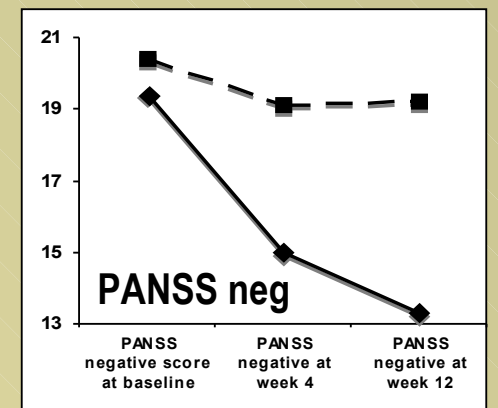
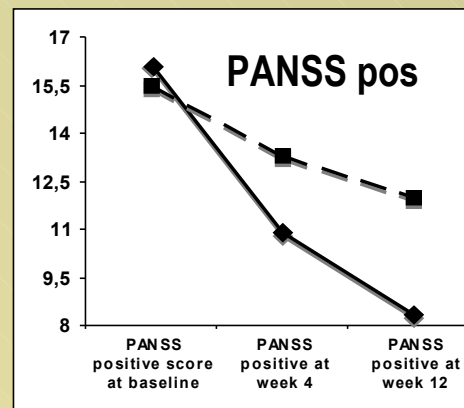
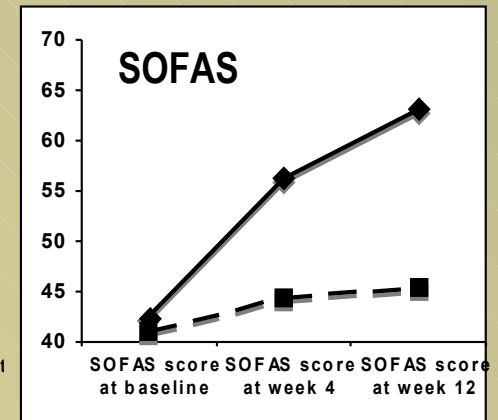
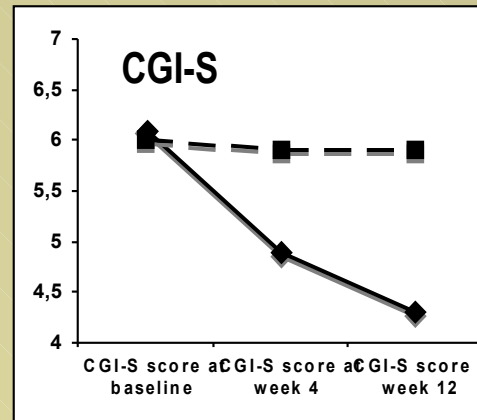
Symptomatic Remission	Functional Remission	SWN Remission	%
No	No	No	35.1
Yes	No	No	11.1
No	Yes	No	7.2
No	No	Yes	8.3
Yes	Yes	No	4.4
Yes	No	Yes	18.9
No	Yes	Yes	2.2
Yes	Yes	Yes	12.8

Early detection of incomplete remission with the SWN-K ¹

727 patients with SWN-K ≤ 60 at admission, treated with amisulpride for 12 weeks



SWN-K response = increase $\geq 20\%$



1. Lambert et al. Acta Psychiatrica Scand, 2006.

HRQoL (SWN-K) as predictor of response (II) ¹

631 patients, 12 weeks follow-up PANSS pos & neg, CGI-S, SOFAS, and SWN-K were transformed into measures ranging from 0-100 and added to a combined outcome variable (=OUT)

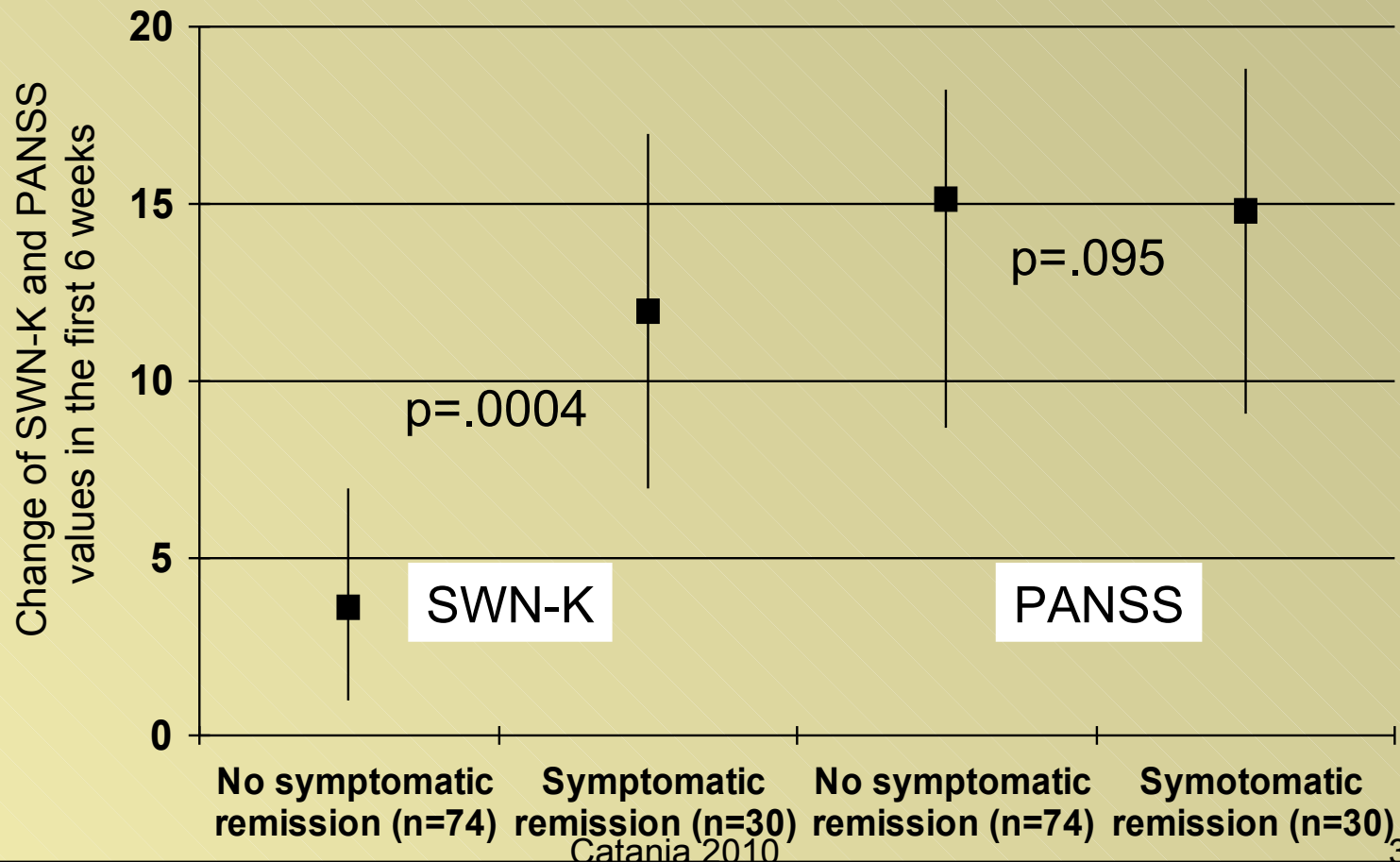
Measure	Beta	T	p
PANSS T0	,14	3,28	,001
CGI T0	,13	3,11	,002
SOFAS T0	,22	5,12	,000
SWN-K T0	,06	1,45	,15

Measure	Beta	T	p
Change T0 to T4			
PANSS	,09	2,21	,027
CGI	,19	4,99	,000
SOFAS	,15	4,08	,000
SWN	,44	10,69	,000

Linear regression of baseline scores with OUT at 3 months

Prediction of 5-year remission by a comparative application of PANSS and SWN-K ¹

- 110 patients with first episode of schizophrenia
- Continuous symptomatic remission between month 6 and month 60



Catania 2010

34

Relationships among SWN and other outcome measures in schizophrenia

(Chen et al. 2010)

- Data of a randomised multi-centre study of chronic schizophrenia patients (n=628) were examined to investigate the relationship among several outcome measures, including PANSS, MADRS, Schizophrenia Objective Functioning Instrument (SOFI), Quality of Life Scale (QLS), and the SWN.
- Two analytic approaches were used: 1) pairs analysis and 2) factor analysis.
- Findings suggest some redundancy, particularly among the clinician-rated functional and quality of life measures. Only a small proportion of the variance in SWN was explained by the clinician-rated measures, suggesting that the SWN captures unique information.

Antipsychotic efficacy without D2 blockade?

- All current antipsychotics are dopamine antagonists or partial antagonists.
- They block (to a different degree) dopaminergic systems relevant for reward behaviour.

Conclusions

- When evaluating the effects of antipsychotic drugs, other psychopharmacological or psychosocial treatment, the assessment should not only include psychopathology but also subjective quality of life.
- Disease-specific scales should be preferred. In patients, no more acutely psychotic and without relevant cognitive deficits, their perspective is fully explored only by self-rated scales.
- Subjective quality of life/ well-being is strongly related to compliance and to the chance of remission.