International Society for CNS Clinical Trials and Methodology

Satellite Meeting on the NIMH Initiative Regarding Treatment Development for Negative Symptoms

Washington DC, USA

February 23-24, 2006

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Epidemiology and Long-Term Course of Negative Symptoms

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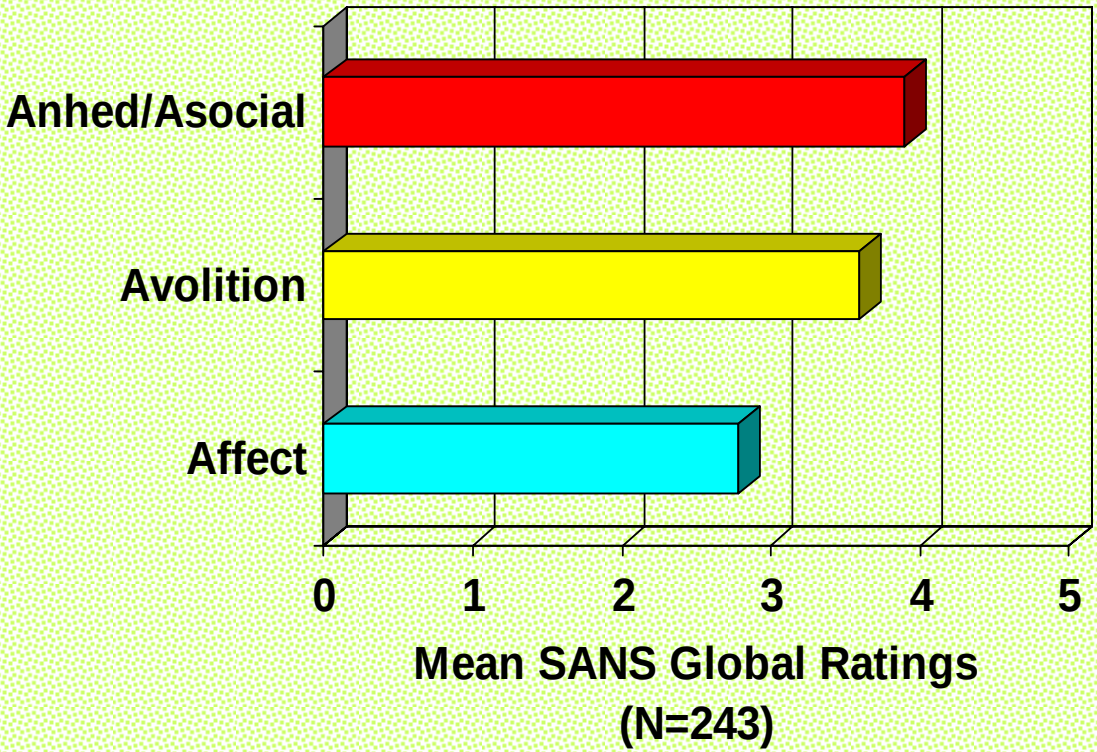
Outline

- Distribution of negative symptoms within schizophrenia
- Negative symptoms in 1st episode patients
- Long-term course of negative symptoms
- Functional impact of negative symptoms
- Prognosis of negative symptoms
- Impact of negative symptoms on quality life and outcome
- Treatment of negative symptoms
  - Review of negative symptom trials
  - Advances to treatment of negative symptoms

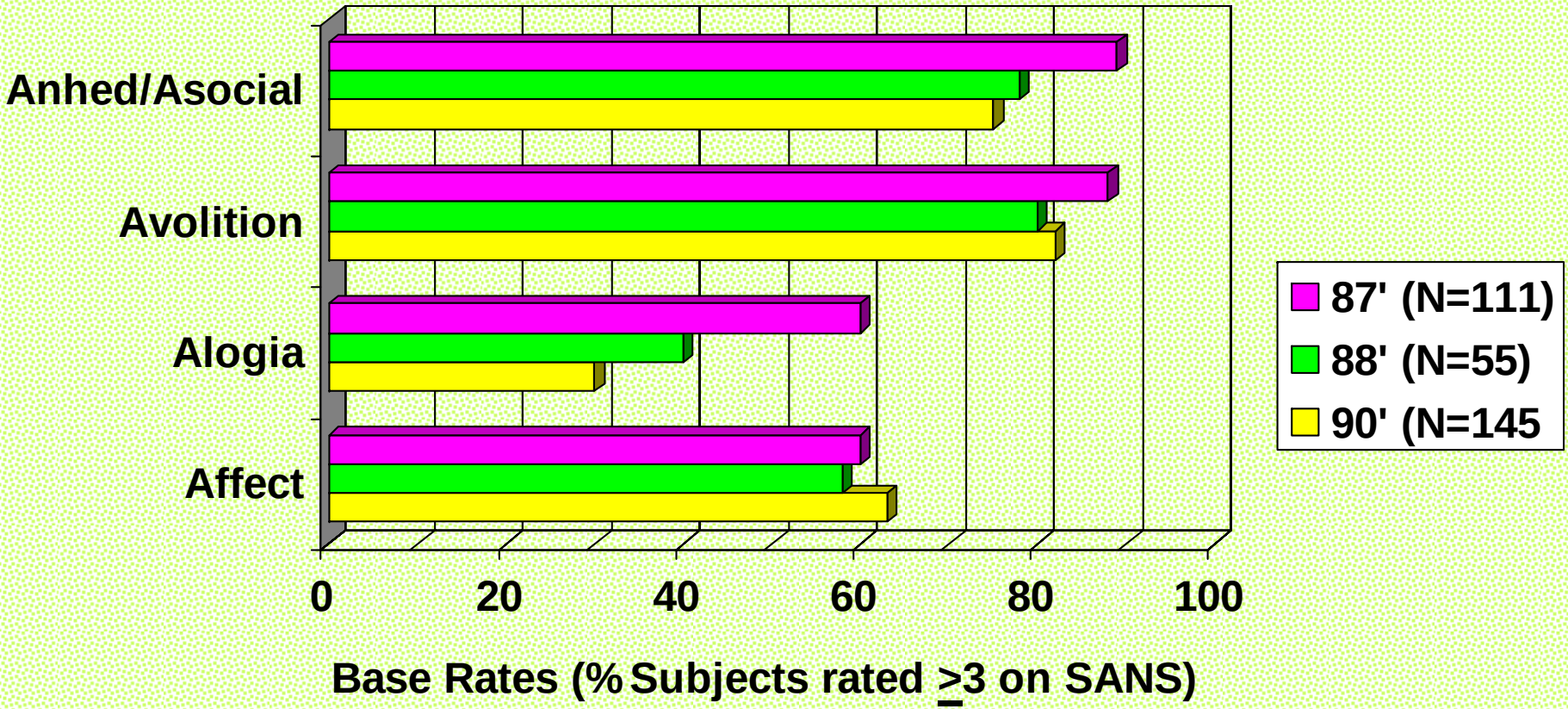
Ratings of Negative Symptoms In DSM-IIIR Schizophrenia



Age 32.0 ± 10.6 yrs.; 69.5% Male; Duration of illness 11.1 ± 9.8 yrs.

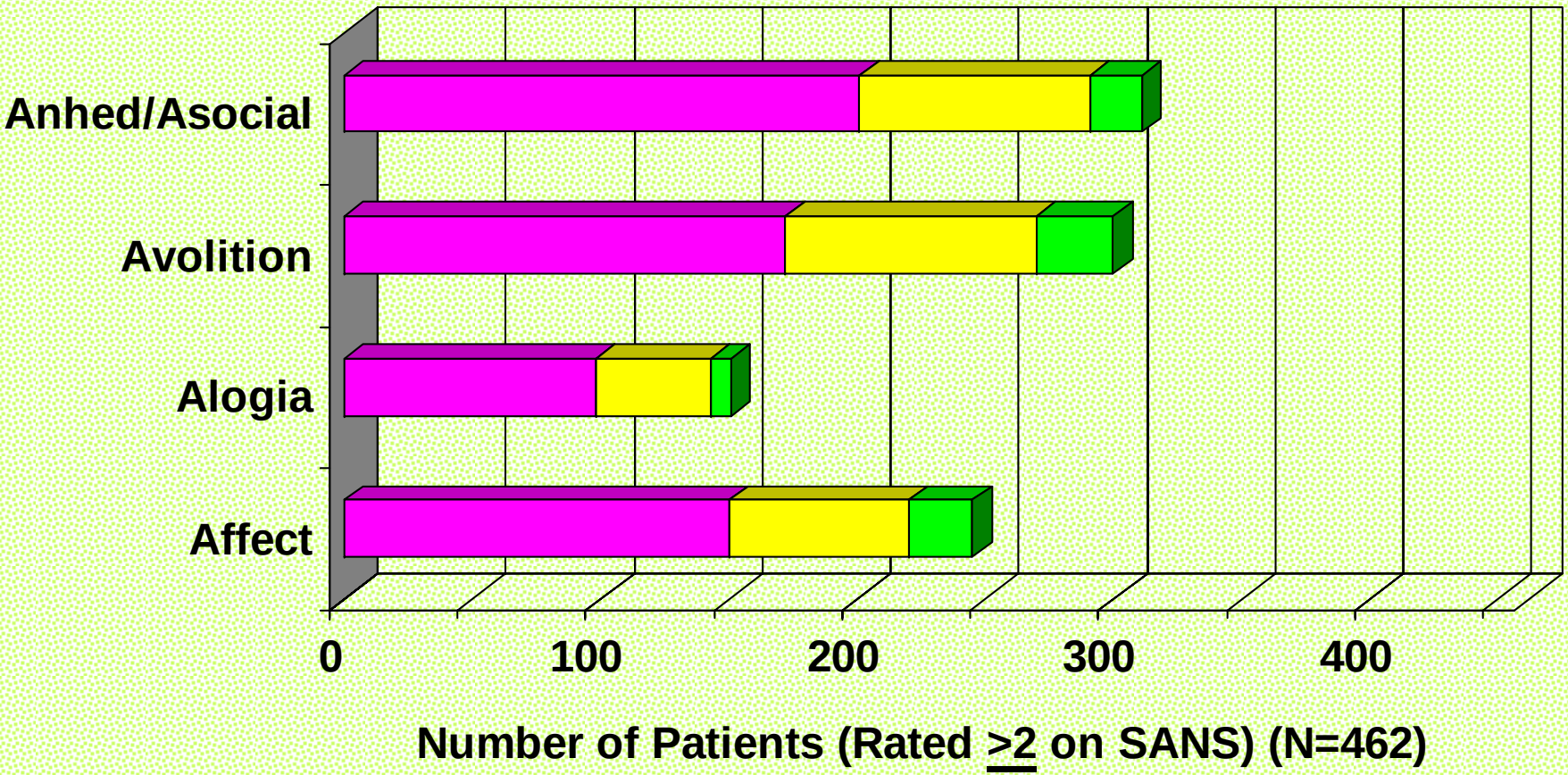
Andreasen NC, et al. *Arch Gen Psych* 52: 341-351, 1995

Frequency of Negative Symptoms In 3 Samples of DSM-III Schizophrenia



Andreasen NC. *Schizophr Bull,* 13: 9-22, 1987

Frequency of "Primary" and "Secondary" Negative Symptoms



Age 33.8 ± 12.3 yrs.; 61.8% Male; Duration of illness 10.7 ± 9.7 yrs.

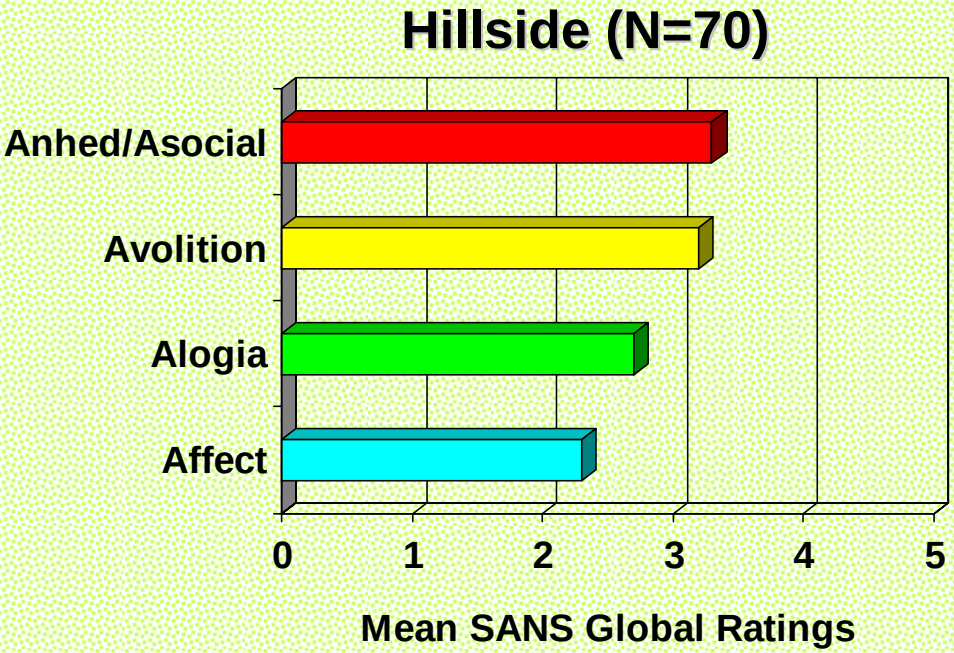
Flaum M and Andreasen NC. *Comp Psych*, 36 (6): 421-427, 1995

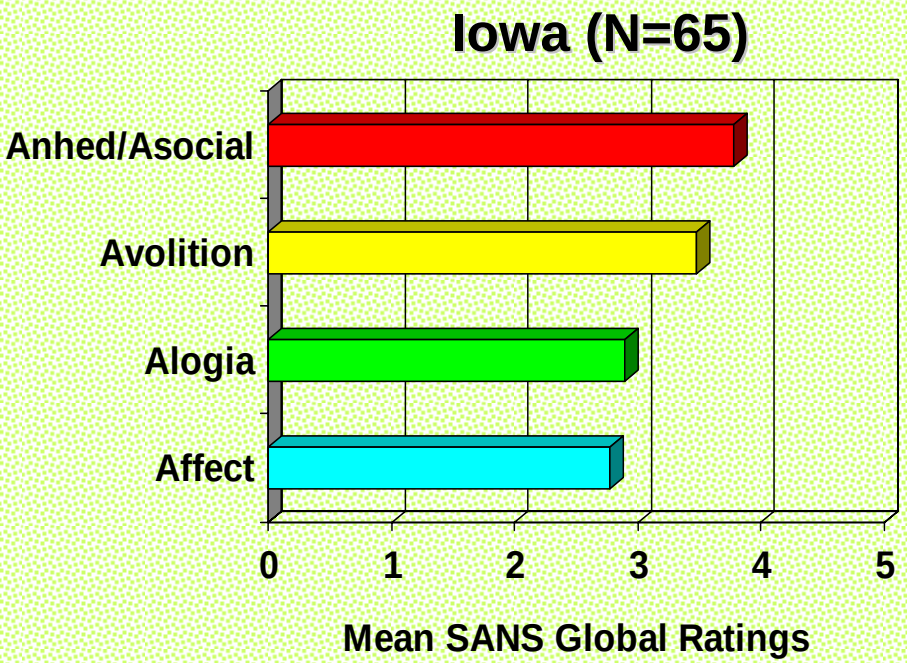
Deficit Syndrome

- Carpenter and colleagues have proposed the "deficit syndrome" as a putative schizophrenia subtype defined by negative symptoms
- negative symptoms in the deficict syndrome are persistent rather than transitory and not due to paranoia, other psychotic symptoms, depression, or antipsychotic akinesia
- Prevalence of deficit syndrome
  - 15% of 1st episode patients
  - 25-30% of chronic populations

Carpenter WT, et al. *Arch Gen Psych* 58: 165-171, 2001

Ratings of Negative Symptoms In 1st Episode Patients





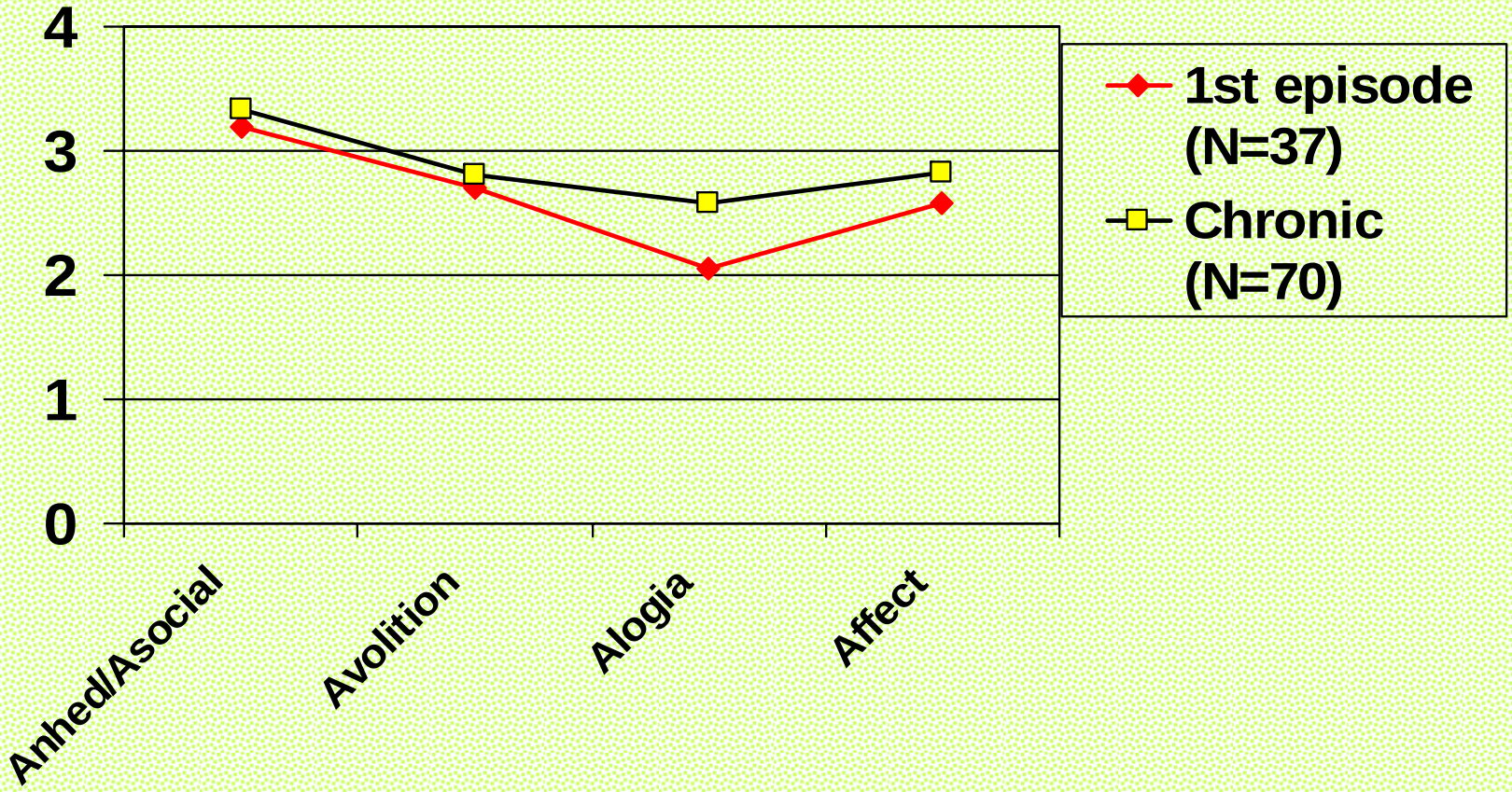
Age 23.9 ± 5.7 yrs.; 56% Male;
Duration of illness 53 ± 53 wks.

Age 24.2 ± 5.2 yrs.; 77% Male;
Duration of illness 8.3 mos.

Lieberman J, et al. *Schiz Bull* 18(3): 351-371, 1992
Arndt S, et al. *Arch Gen Psych* 52: 352-360, 1995

Ratings of Negative Symptoms In 1st Episode vs. Chronic Patients

Mean SANS Global Ratings



Shtasel DL, et al. *Schiz Bull* 18(3): 449-462, 1992

Longitudinal Study of Symptoms in 1st Episode Patients

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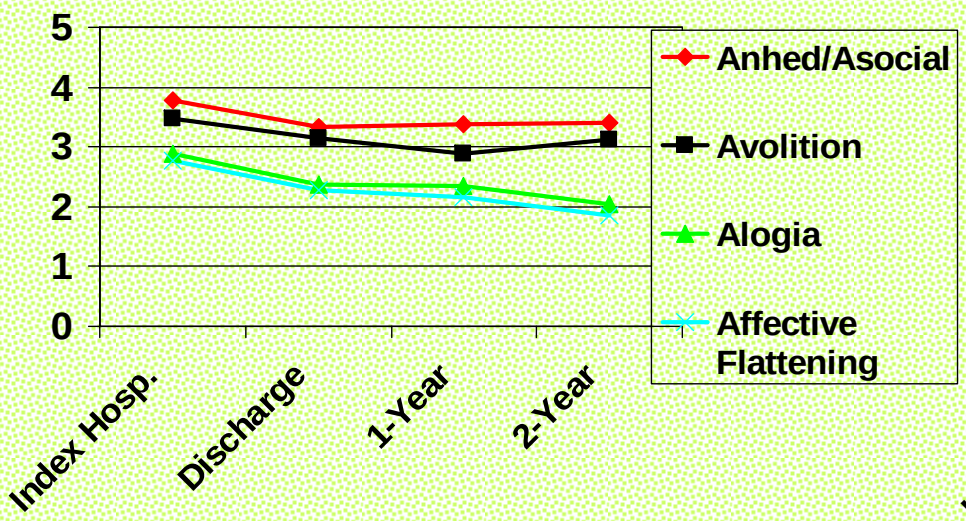
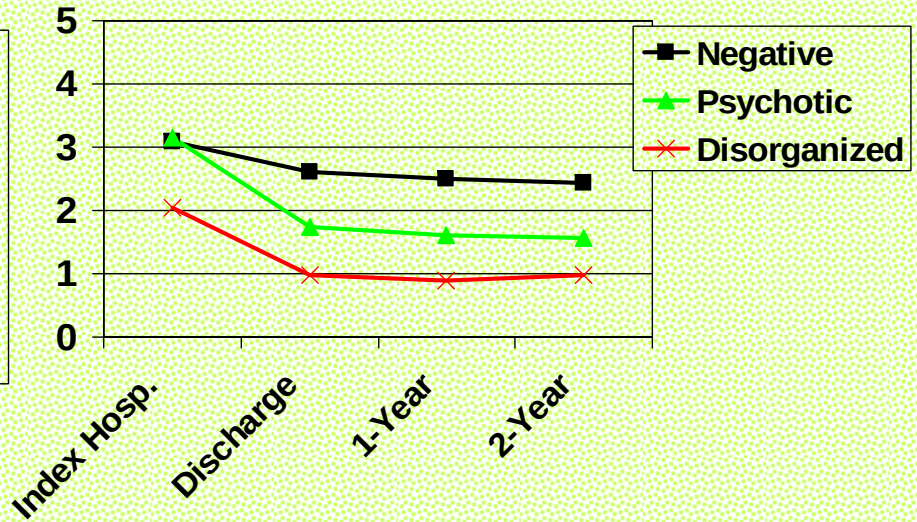
Mean SANS Global Ratings (N=65)

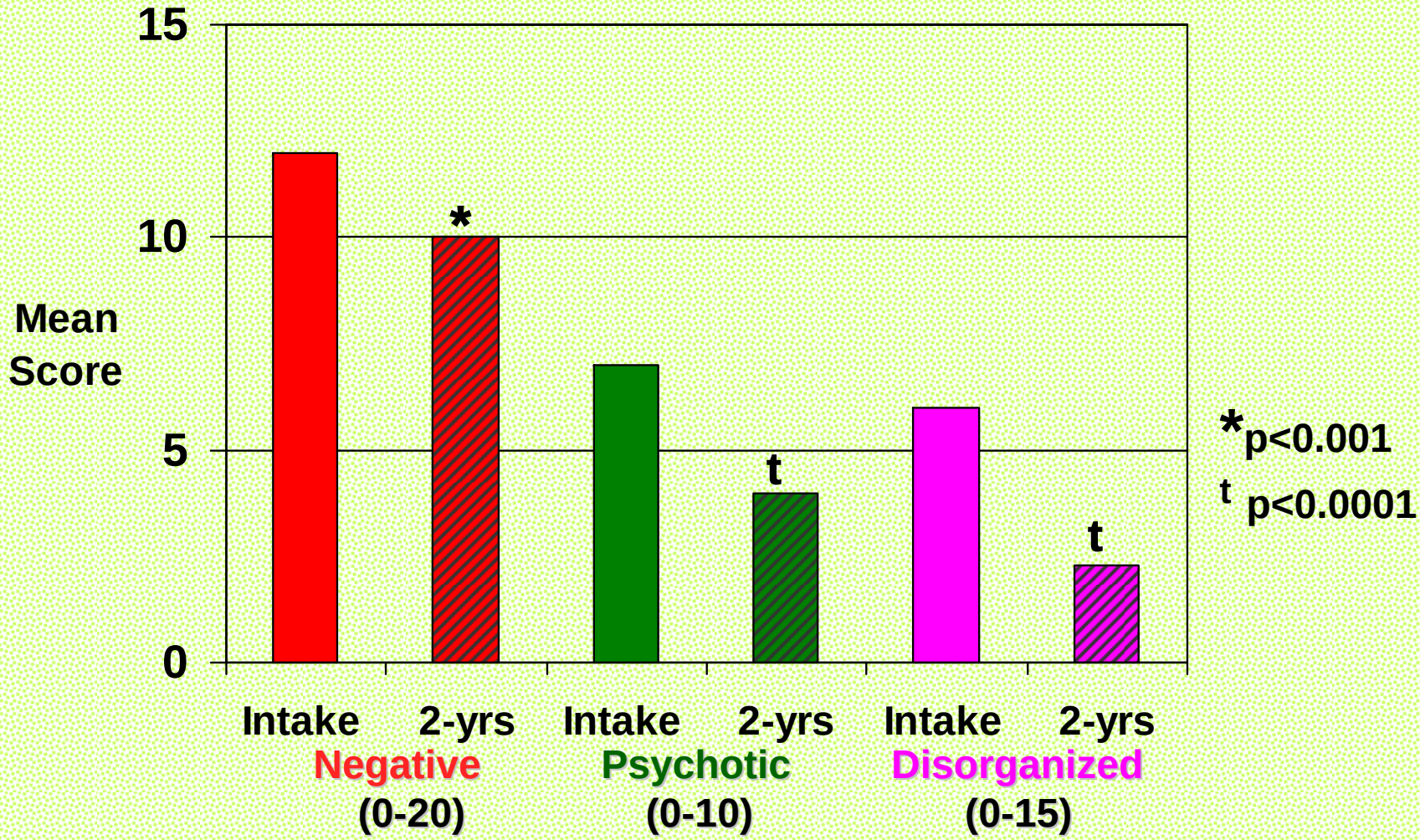


Mean SAPS/SANS Factor Ratings (N=65)



Arndt S, et al. *Arch Gen Psych* 52: 352-360, 1995

Two-Year Outcome in 1st Episode Schizophrenia



Ho BC, et al. Am J Psych 155(9):1196-1201, 1998

Correlations of Symptoms Ratings at Index Hospitalization and Outcome at 2-yrs. (p-values)

Outcome Measure	Negative	Psychotic	Disorganized
Occupational Impairment	0.03	0.32	0.48
Financial Dependence	0.001	0.01	0.68
Impairment in household duties	0.02	0.33	0.96
Relationship impairment			
Family	0.14	0.24	0.61
Friends	0.01	0.51	0.59
Enjoyment of recreational activities	0.01	0.59	0.22
Overall psychosocial function	0.004	0.06	0.76
GAS score	0.03	0.08	0.99

Ho BC, et al. Am J Psych 1 155(9):1196-1201, 1998

Outcome in Washington IPSS Cohort

2-Years Follow-up

- Initial poor interpersonal relations were significantly correlated with fewer social contacts, increased symptoms and total poor outcome

5-Year Follow-up

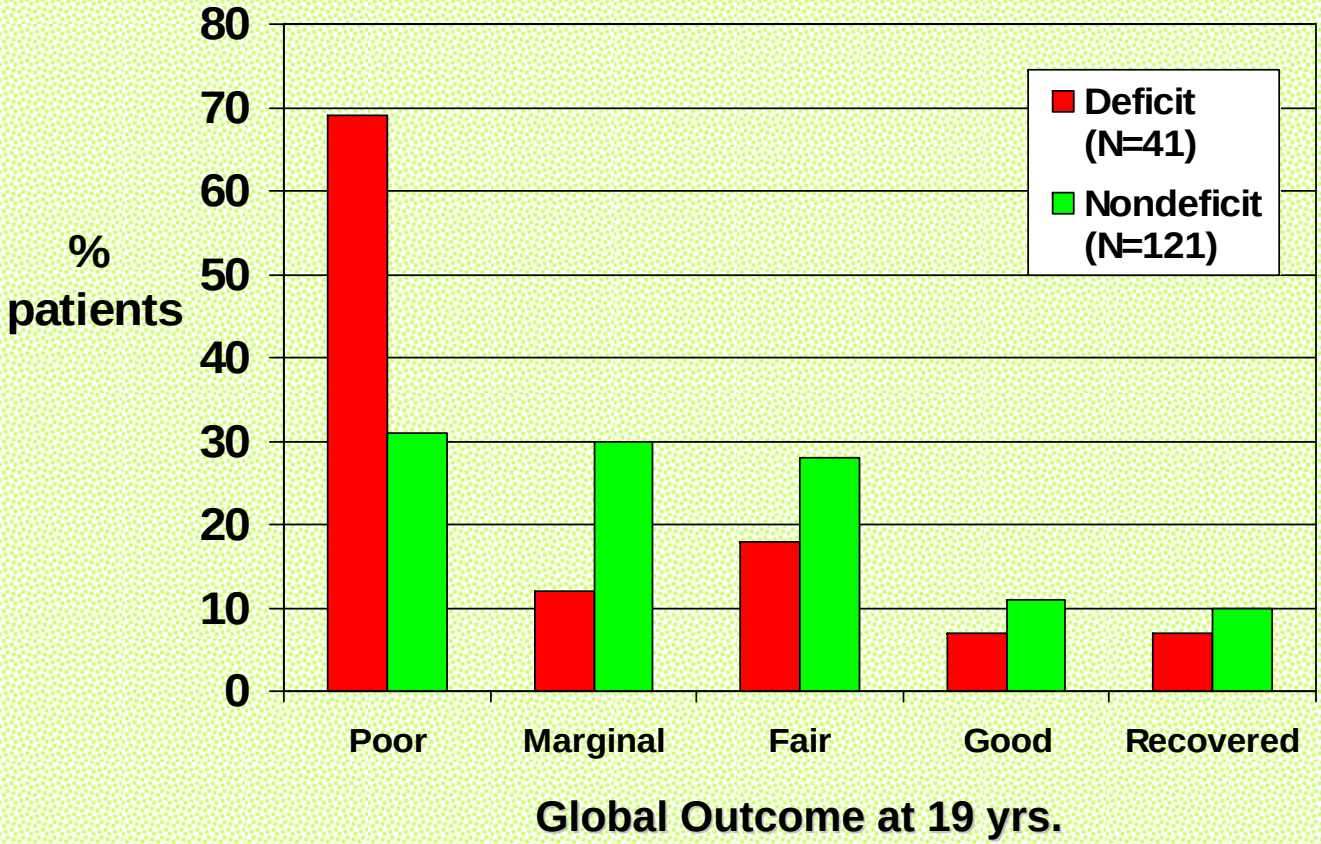
- Initial poor interpersonal relations were significantly correlated with fewer social contacts, less employment, increased hospitalization and symptoms, and total poor outcome
- Initial restricted affect significantly correlated with poor outcome

11-Year follow-up

- Initial poor interpersonal relations were significantly correlated with fewer social contacts, less employment, increased symptoms, and total poor outcome
- Initial restricted affect not correlated with poor outcome

Strauss & Carpenter. Arch Gen Psychiatry 30: 429-434, 1974
Strauss & Carpenter. Arch Gen Psychiatry 31: 37-42, 1974
Carpenter WT, et al. *J Nerv Ment Dis* 179(9): 517-525, 1991

Long-Term Outcome of the Deficit Syndrome in Schizophrenia



- Fewer deficit pts. married before onset
- Negative sxms present at onset in deficit pts. and increased over 5 yrs
- Deficit syndrome highly stable
- No deficit pts. committed suicide

Fenton & McGlashan. *Am J Psych* 151:351-356, 1994

Treatment of Negative Symptoms: Antidepressants

Drug	N	Subject Status	Duration	Control	Results
Fluoxetine Spina 94'	34	Chronic	12 wks	Placebo	(-) Flu > Plc (+) NS (depr.) Flu>Plc
Citalopram Taiminen 98'	75	Chronic	12 wks	Placebo	(-) NS; (+) NS (depr.) NS
Fluvoxamine Silver 98'	25	Prominent (-) sxms	6 wks	Maprotyline	(-) Flu > Map (+) NS (depr.) NS
Mirtazepine Berk 01'	30	Chronic	6 wks	Placebo	(-) Mir > Plc (depr.) NS
Reboxatine Schutz 01'	30	Chronic	6 wks	Placebo	(-) NS; (+) NS (depr.) NS

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Treatment of Negative Symptoms: Glutamate Agonists

Drug	N	Status	Duration	Control	Results
Glycine Javitt 99'	22	Resistant	6 wks, crossover	Plc	(-) Gly > Plc (BPRS) Gly > Plc (depressive) NS
D-cycloserine Goff 99a'	57	Deficit	8 wks	Plc	(-) DCS > Plc; (+) NS (depressive) NS (cognition) NS
D-cycloserine Evins 02'	10	Deficit	2 wks Plc, & 2 wks- 4 doses DCS		(-) DCS 50 mg > Plc (depressive) NS (cognition) NS
D-cycloserine Glycine Carpenter 04'	171	Prominent (-) sxms	16 wks	Plc	(-) NS; (+) NS (cognition) NS

- DCS and glycine added to clozapine resulted in a worsening of negative symptoms (Goff et al, 1999b; Evins et al, 2000)

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Treatment of Negative Symptoms: Antipsychotics

Drug	N	Status	Duration	Control	Results
Risperidone Marder 93'	338	Acute	8 wks	Haloperidol Placebo	(-) R6, 16=Plc >H (+) R & H > Plc (EPS) R6 = Plc<H
Olanzapine Beasley 96'	335	Acute	6 wks	Haloperidol Placebo	(-) O > H & Plc (+) O & H > Plc (EPS) O < H
Quetiapine Arvanitis 97'	361	Acute	6 wks	Haloperidol Placebo	(-) Q = H > Plc (+)Q300 = H > Plc (EPS) Q = Plc< H
Ziprasidone Daniel 99'	302	Acute	6 wks	Placebo	(-) Z > Plc (+) Z > Plc (EPS) Z = Plc
Aripiprazole Potkin 03'	404	Acute	4 wks	Risperidone Placebo	(-) A = R > Plc (+) A = R > Plc (EPS) A = Plc = R

Treatment of Negative Symptoms: Antipsychotics

- The results of these studies must be interpreted cautiously as most were not designed specifically to evaluate "primary" negative symptoms and did not control for improvement in other symptoms
- Both risperidone and aripiprazole have shown superiority over haloperidol for negative symptoms in 1-year studies (Csernansky et al, 2002; Kasper et al, 2003)

Treatment of Negative Symptoms: Antipsychotics

- In a 16-wk study in subjects with residual positive and negative symptoms, olanzapine was not superior to haloperidol for negative symptoms (Buchanan et al, 1998)
- Two longer-term studies in subjects with residual symptoms failed to show a difference between clozapine and haloperidol in negative symptoms (Buchanan et al, 1998; Kane et al, 2001)
- Studies specifically designed to evaluate negative symptoms were generally small, had low base rates on negative symptoms, and included refractory subjects

Treatment of Negative Symptoms: Antipsychotics

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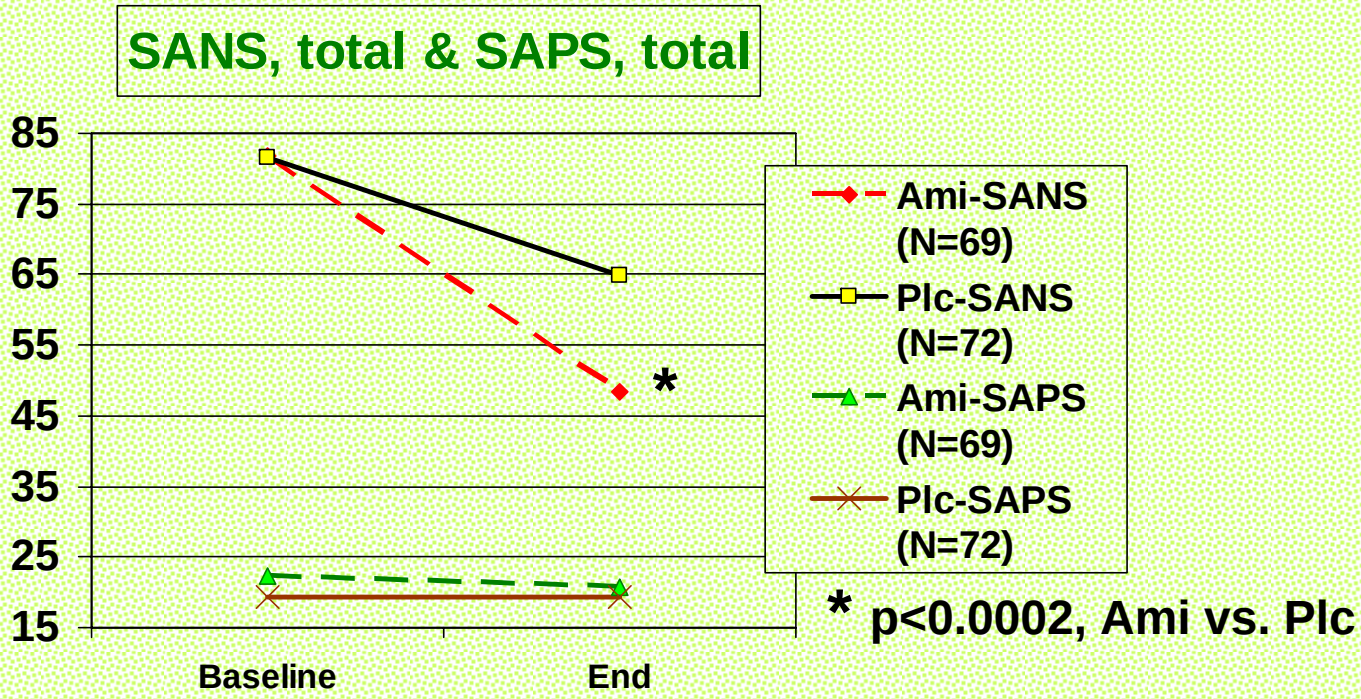
Path Analyses

- Used to statistically evaluate the direct and indirect effects of treatment on negative symptoms, accounting for changes in positive symptoms, mood, and EPS
- Risperidone and olanzapine have been shown to improve negative symptoms to a significantly greater extent than haloperidol after controlling for these indirect effects (Moller et al, 1996; Tollefson et al, 1997)
- These data are supportive, but cannot be relied upon to disentangle effects on primary negative symptoms from other secondary sources of variance (Kirkpatrick 2000)

Treatment of Negative Symptoms: Amisulpride

- Randomized, parallel-group, double-blind study comparing amisulpride 100mg/day vs. placebo for 6 mos.; ITT analyses
- N=141, predominantly negative symptoms (SANS≥60, SAPS≤50)



Loo et al. *Br J Psych* 170: 18-22, 1997

Treatment of Negative Symptoms: Amisulpride

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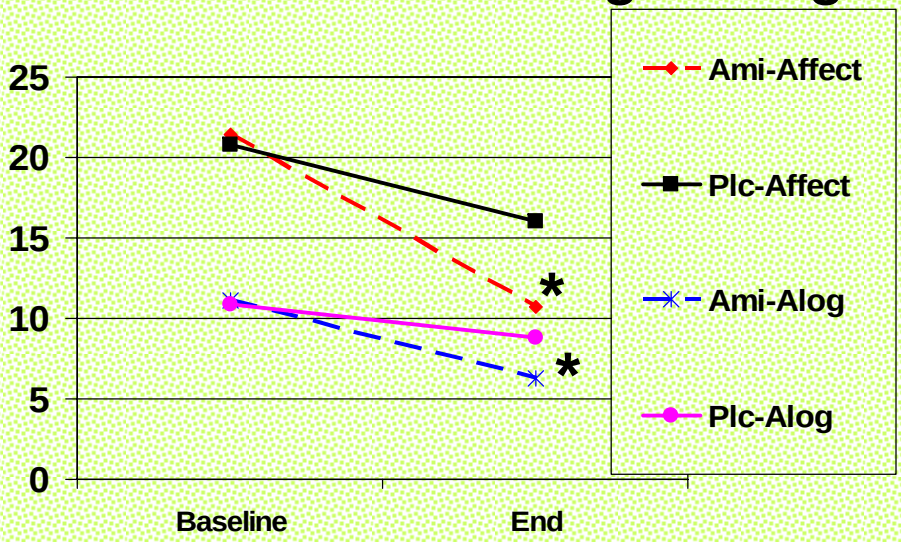
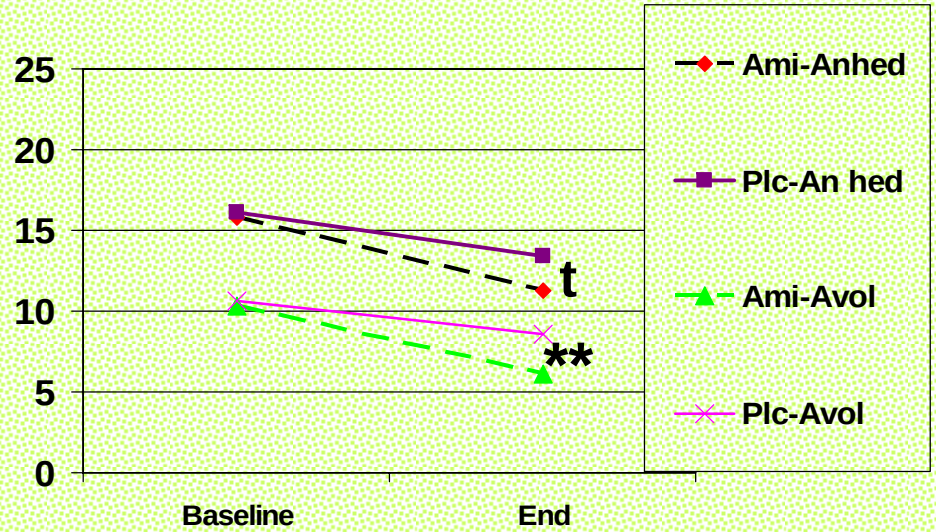
Affective Flattening & Alogia



Anhedonia & Avolition



* p<0.0002, Ami vs. Plc

** p<0.0007, Ami vs. Plc

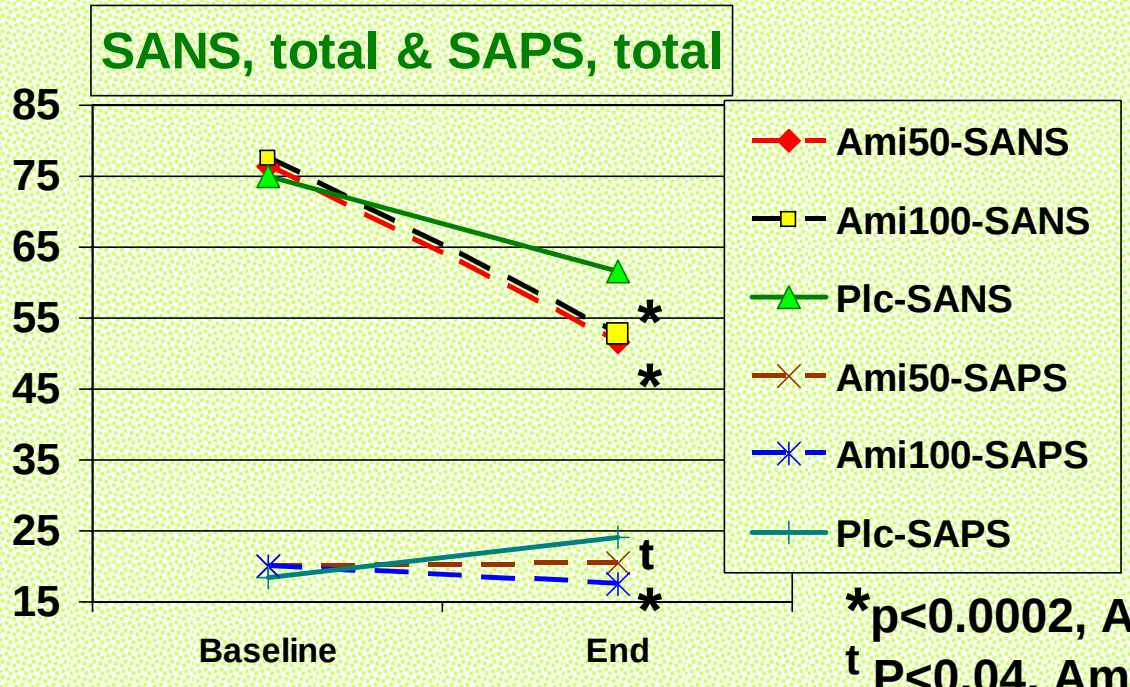
t p<0.005, Ami vs. Plc

- The % of amisulpride pts. completing the study (56%) was significantly higher than with placebo (32%)

Loo et al. *Br J Psych* 170: 18-22, 1997

Treatment of Negative Symptoms: Amisulpride

- Randomized, parallel-group, double-blind study comparing amisulpride 50mg/day (N=84) or 100mg/day (N=75) vs. placebo (N=83) for 12 wks.; ITT analyses
- Predominantly negative symptoms (SANS≥60, SAPS≤50)



*p<0.0002, Ami vs. Plc
t P<0.04, Ami50 vs. Plc

Danion et al. *Am J Psych* 156: 610-616, 1999

Conclusions

- Negative symptoms are ubiquitous in schizophrenia, beginning early in the illness and continuing throughout the illness
- Negative symptoms are associated with significant impairment in functioning and are related to poor psychosocial outcomes

Conclusions

- While the newer antipsychotics have been shown to be of benefit in treating negative symptoms, patients continue to suffer with significant impairments
- Negative symptoms remain a great unmet therapeutic need