Cultural issues in psychiatric outcomes for global trials

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General problems of rating scales ("soft outcomes")

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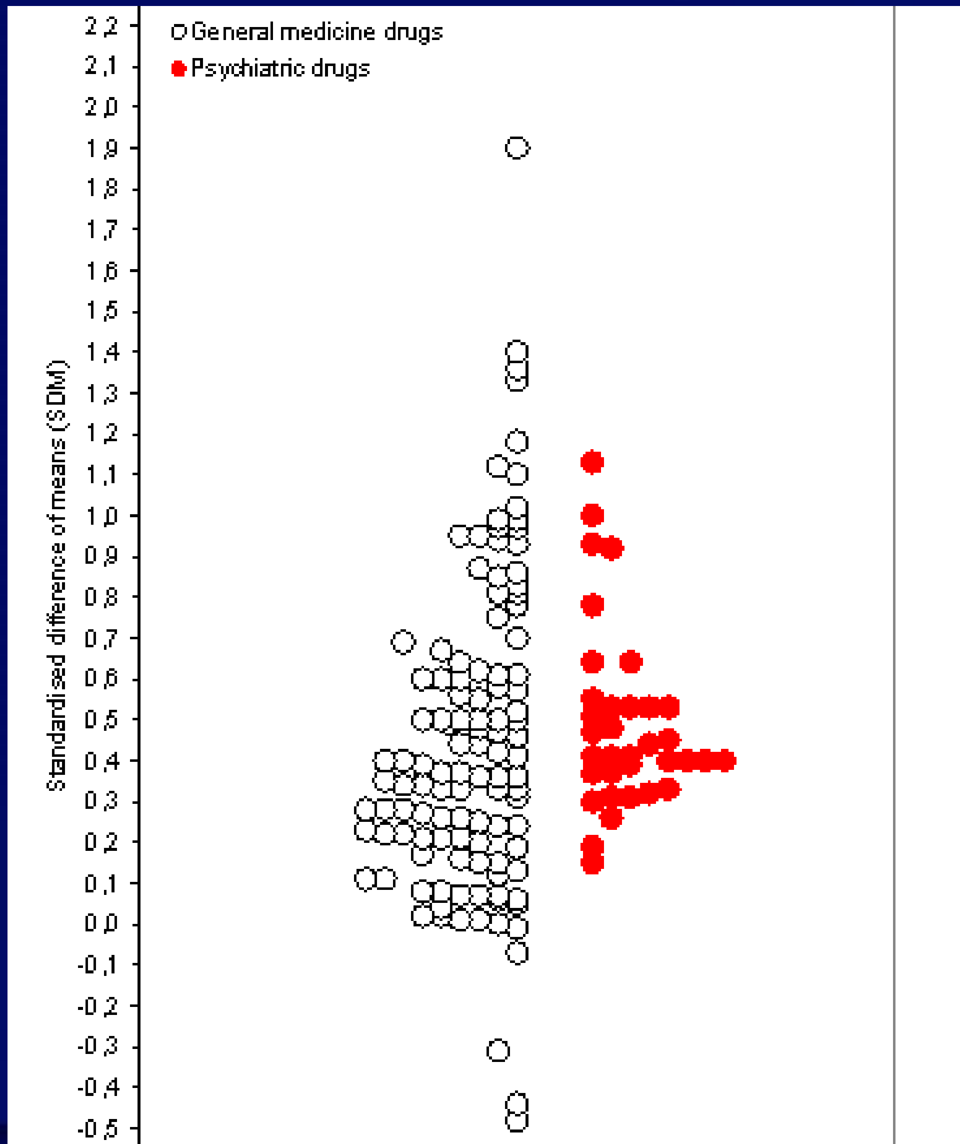
General problems of rating scales ("soft outcomes")

- They are subjective and "soft"
- They are difficult to interprete clinically
- They are subjective to cultural variations

(for example the content of hallucinations can differ based on the cultural environment (Laroi et al. Schizophrenia Bulletin 2014), and for delusions this is even more well known.

Effect sizes of general medicine and psychiatric drugs



Review of 91 meta-analyses on 48 general medicine drugs and of 33 meta-analyses 16 on psychiatric drugs

Leucht et al.
Br J Psychiatry, 2012

Major depressive disorder – acute episode

Therapy	Outcome	Mean weeks	N	n	% PBO	% Drug	Response difference	NNT	Response ratio
Paroxetine	Response	7.5	22	5112	**42.2**	**53.2**	**10%**	10	20%
TCAs	Response	6	32	4314	**31**	**46**	**15%**	7	50%

Therapy	Outcome	Mean weeks	N	n	Raw units	Effect size
Paroxetine	**HAM-D**	7.5	34	5764	2.62	**0.31**

Barbui et al. CMAJ 2008
Storosum et al. Eur Neuropsychopharmacol 2001

Schizophrenia acute treatment

Therapy	Outcome	Mean weeks	N	n	% PBO	% Drug	Absolute Response difference	NNT	Response ratio
Second generation antipsychotics	Response	9	28	4498	23.7	40.6	18%	6	70%

Leucht et al. Molecular Psychiatry 2009

ACE inhibitors for long-term treatment of hypertension

Outcome	Mean weeks	N	n	% PBO	% Drug	Absolute risk difference	NNT	Relative risk reduction
Cardiovascular events	3.9 years	5	18229	**18.1**	**14.1**	**4%**	25	22%

Blood Pressure Lowering Treatment Trialists' Collaboration, Lancet 2003

Prevention of cardiovascular disease and stroke by statins

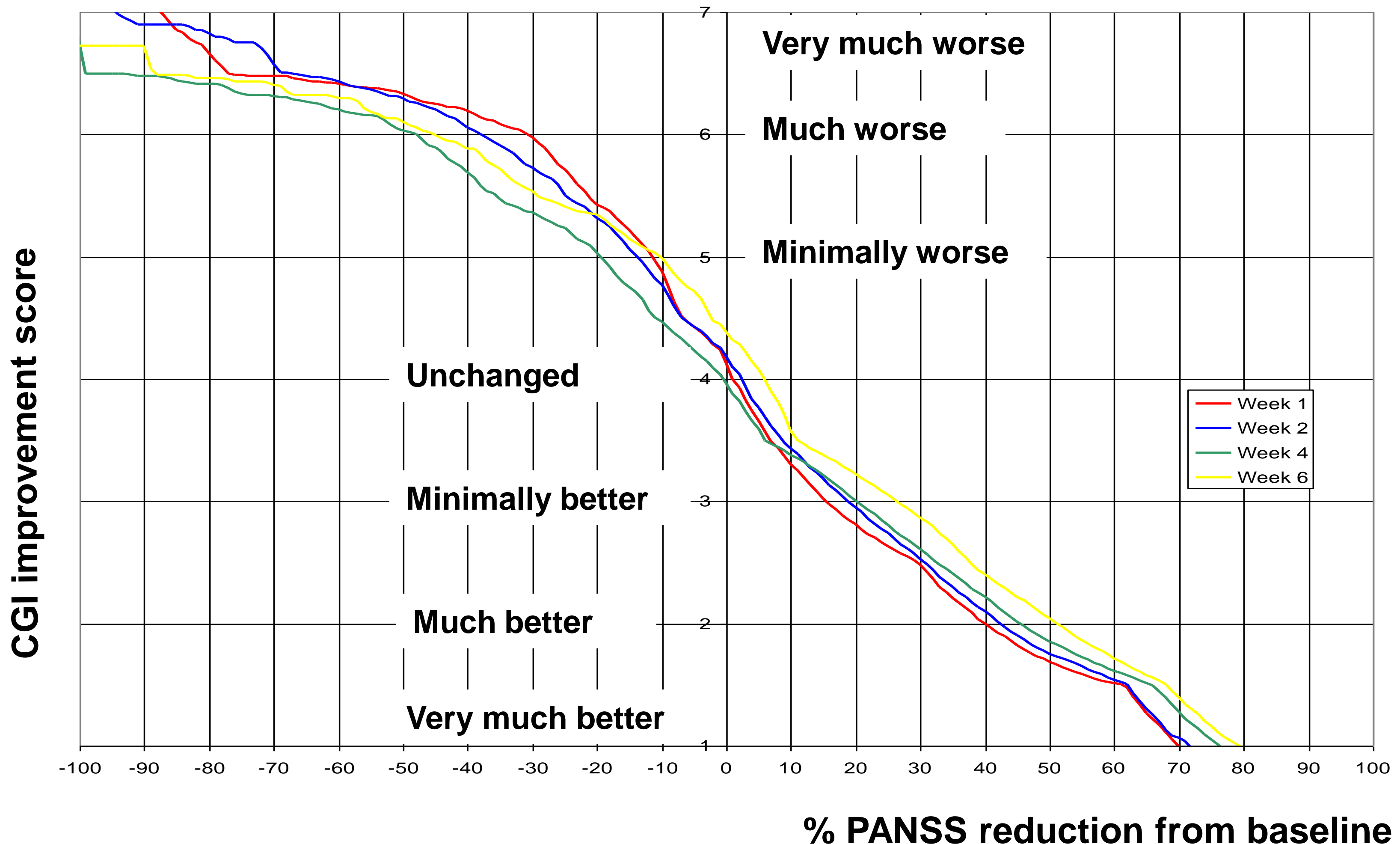
Therapy	Outcome	Mean weeks	N	n	% PBO	% Drug	Risk difference	NNH	Relative risk reduction
Statins	**Major cardiovascular events**	5 yrs	14	90056	**17.8**	**14.1**	4%	27	21%
Statins	**Mortality**	5 yrs	14	90056	**9.7**	**8.5**	1.2%	83	12%

Baigent et al. Lancet 2005

Suggestion 1: Consensus on definitions

- Come up with consensus on definitions on simple concepts such as response, remission, relapse.
- For example, many definitions of response have been used in schizophrenia (at least 20%, 30%, 40% or 50% reduction of PANSS total score)
- This consensus should be achieved with appropriate procedures (e.g. delphi process), but also use evidence

Linking of CGI Change with Percent Reduction of PANSS Total Score from Baseline (n=1231)



Leucht et al. Schizophrenia Research 2005

Leucht et al. Neuropsychopharmacology 2006

Suggestion of a simple table for the display of BPRS/PANSS derived response rates

	Total n	≤0 % PANSS/BPRS reduction	1% - 24% PANSS/BPRS reduction	25% - 49% PANSS/BPRS reduction	50% - 74% PANSS/BPRS reduction	75% - 100% PANSS/BPRS reduction	Remission
Intervention Group	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Control Group	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Leucht et al. Neuropsychopharmacology 2007

Leucht and Kane Journal of Clinical Psychiatry 2006

Leucht J Clin Psych 2014

Global Expert Working Group

Criteria Foundation: Illness symptoms

Delusions	Delusions (P1)
	Unusual thought content (G9)
Hallucinations	Hallucinatory behavior (P3)
Disorganized speech	Conceptual disorganization (P2)
Grossly disorganized or catatonic behavior	Mannerisms/ posturing (G5)
Negative symptoms	Blunted affect (N1)
	Social withdrawal (N4)
	Lack of spontaneity (N6)

Severity criterion:

All 8 symptoms mild or better

Time criterion:

For at least 6 months

Andreasen et al Am J Psychiatry 2005
Van Os et al. Acta Psychiatr Scand 2006

Suggestion 2: Produce systematic reviews and comparative trials on rating scales

- In many domains different rating scales are available. If we knew which is the most appropriate one and if all studies used them, this would make results more comparable
- Produce systematic reviews and maybe even comparative trials on rating scales for each domain to understand which is the best one for which situation.
- Example: Many rating scales on negative symptoms have recently been developed. But which one is the "best" one and what are the important differences between them is unclear.

ASSESSMENT OF NEGATIVE SYMPTOMS

SANS (Andreasen et al. Br J Psychiatry Suppl. 1989)

PANSS negative subscore (Kay et al. 1994)

PANSS negative factor ("Marder factors" Marder et al. J Clin Psych 1997)

NSA-16 Negative Symptom Assessment (Axelrodt et al. J Psychiatr Res 1993)

Clinical Assessment Interview for Negative Symptoms (CAINS, Forbes et al. Schizophr. Res. 2010)

Brief Negative Symptoms Scale (Kirkpatrick et al. Schizophr Bull 2011)

CGI for negative symptoms (Haro et al. Acta Psychiatr Scand Suppl. 2001)