Evidence based practise in child- and adolescent psychiatry

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Lecture 1: what is evidence, why is it important and what is its relation to priority.
Lecture 2: the Swedish National Board of Health and Welfare (Socialstyrelsen) and its work with clinical guidelines: methods (GRADE) and procedures.
Lecture 3: examples of recent guidelines in affective- and anxiety disorders.

Lecture 1: a/what is evidence, b/why is it important and c/what is its relation to priority.

- The resorces of the society are limited, only forms of practice that actually work are to be sponsored
- Society has a responsibility to pay only for practise that is beneficial and do not harm
  - Society provides guidelines to make it clear to those who organize care what methods are to be provided (in Sweden, the National Board of Health and Welfare)
  - Society provides guidelines for individual clinicans on what methods to use (In Sweden: Drugs - the Medical products Agency; medical appliances (e.g., pacemakers) – none; psychological therapies - none
  - Certified doctors, nurses, psychologists, psychotherapists … are bound by their certification to use only methods that are beneficial and do not harm
- We as clinicians as well wish to help and not to harm
- The need for evidence follows from points above

Additional demands within the Swedish national guidelines

- To use resources in the most effective way
- To provide good care and treatment for all in a fair way and on equal terms for all citizens
- Develop and monitor high quality in all levels of care

To use resources in the most effective way

What is evidence ?

Efficacy/effectiveness

Efficacy

- Does a treatment have an effect that is so large as compared with all other sources of variance that the signal stands out?
- Statistical significance is the first prerequisite

Effectiveness

- Is the treatment effect as those measured in an efficacy study of clinical significance?
- Is it possible to perform the intervention in real life with ordinary clinicians?
- Can the treatment be used with the patients the clinicians see in the clinics?
- Is the treatment applicable with the patients seen in the clinic?

To use resources in the most effective way

What is evidence ?

Who are those we want to treat?

- What problem/disorder: use of DSM 5 ensures the disorder is clinically similar if not identical
  - A diagnostic system that is valid
  - Procedures to ascertain are valid and reliable
  - The severity is comparable
- What characterizes those that have the problem/disorder:
  - Age group & gender is appropriate
  - Culture, Socioeconomical situation, etc are reasonably similar
  - Experience, factors that contributes to the disorder/treatment etc are reasonably similar
  - Genetic differences across ethnical groups may affect both pharmacodynamics and kinetics

To use resources in the most effective way

What is evidence ?

Which intervention?

- An intervention need to be described in a way that makes it possible to use in practise
  - Drugs: doses, titration schemes, handling of side effects vs doses, preparation, …..
  - Psychotherapy
    - Manuals that are operationalised so that they can be applied (=surgery)
    - Manuals that allows flexibility
    - Manuals that operationalizes the theoretical underpinning of the treatment

To use resources in the most effective way

What is evidence ?

Are comparisons relevant?

- What do we need to control for
  - Time: most disorders fluctuate in intensity across time and parents seek care when sx are worst,
  - Attention: many children and adolescents have too little, and most thrive on attention
  - Unspecific therapeutic effects
    - Psychoeducation about sx and about Tx: realize that thoughts, feelings & behaviours are not necessary or unavoidable;
    - Parents give more attention and cease to do harmful things if somebody external eyes are on them

To use resources in the most effective way

What is evidence ?

The Randomized Controlled Trial (RCT)

- A question on whether an intervention is effective is a question of causality: Intervention -> causes -> outcome
- Only experimental ***S***tudy designs can make causality plausible, thus RCRs are necessary - PICOS
  - ***I***ntervention vs ***C***omparison placebo (pill or psychological) or establ treatment
  - ***P***opulation of interest and relevance
  - ***O***utcome measures that work
- RCT limitations
  - Tend to have limited time frames that minimizes attrition while still giving an adequate signal
  - Tend to use samples that makes a signal (difference Intervention-control) larger with fewer subjects (research economics)
  - Tend to use assessment methods that contributes to a clear signal but which may miss out on other relevant perspectives (e.g., QoL)
  - Side effects, even serious ones, that takes a long time to develop are not detected
  - Trial manuals a compromise between ease of use and efficacy

To use resources in the most effective way

What is evidence ?

Are measurements possible/relevant and psychometrically sound?

- Scepticism in parts of childpsychiatry, particularly psychodynamic proponents
- Diagnoses (DSM 5) using KSADS are valid for most common disorders (LEAD)
- For most diagnoses we have symptom scales that are both valid and reliable with reasonable psychometrics: CY-BOCS, SCARED, MFQ, ASEBA
  - Measure severity of symptoms before and after treatment
  - Inventory of Sx befor and following Tx
- We have good ways to measure impairment in general (CGAS) or for specific disorders (COIS,
- We can measure Quality of Life
- For a discussion see Youngstrom (2016)

Jarbin (2017) Nord J Psychiatry 71(4): 270-276; Lauth (2010) Nord J Psychiatry 64(6): 409-420; Ivarsson (2018) 49(2): 234-243; Skarphedinsson, G., et al. (2018); European Child and Adolescent Psychiatry; Jozefiak (2010) Health Qual Life Outcomes 8: 136; Youngstrom (2016) Clinical Psychology: Science and Practice 23(4): 327-347.

To use resources in the most effective way

What is evidence ?

Are measurements possible/relevant and psychometrically sound?

- All assessment methods have limited accuracy
- Clinical interviews (unstructured) are much less valid and reliable than (semi)structured interviews
- It is possible to handle the limited accuracy of diagnostic methods using different diagnostic methods in sequence and independently adding diagnostic likelihood ratios using Nomograms – it is even easy and fun!
- It is costly to treat based on faulty diagnosis
- Humbleness in diagnostic procedures

Youngstrom (2016) Clinical Psychology: Science and Practice 23(4): 327-347; Rettew (2009) Int J Methods Psychiatr Res 18(3): 169-184; Youngstrom (2014) Journal of Pediatric Psychology 39(2): 204-221;

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To use resources in the most effective way

What is evidence ?

Effectiveness trials (RCT, SMART etc.)

Effectiveness trial

- Few exclusion criteria (so that patients are similar to those in clinics)
- Treatments done in ordinary clinics with clinicians
- Independent assessments
- Outcome data are valid, smaller ES but more fully representative
- Examples: TADS (2004); TORDIA (2008, 2010); IMPACT (2017); CAMS (2008); NordLOTS (2014 – nu)

Efficacy trial

- Many exclusion criteria (to make signal/noise ratio good)
- University clinics, often graduate students as therapists
- Double blinded/blinded as far as possible,
- Outcome data are valid but may be not fully representative of patients
- Examples: drug RCT*

Brent (2008) JAMA **299**(8): 901-913; Goodyer (2017) Lancet Psychiatry **4**(2): 109-119; Emslie (2010) American Journal of Psychiatry **167**(7): 782-791; *Emslie (2002) Journal of the American Academy of Child and Adolescent Psychiatry **41**(10): 1205-1215.

To use resources in the most effective way

What is evidence ?

The Randomized Controlled Trial (RCT)

- Important that all trials are known/registered (ISRCTN, ClinicalTrials.gov) and results available (raw data at e.g. at FDA, NIMH)
  - File drawer problem (hidden negative studies)
  - Societal regulations have tamed the pharmacological industry but not psychotherapy proponents
  - Financing of studies is easier for pharmacology than psychotherapy
- Observational studies, uncontrolled studies and naturalistic designs give information that is complementary to RCTs and endow them with a richer perspective
- Clinics tends to be swayed by new interesting/spectacular methods rather than supporting clinical follow-up studies

To use resources in the most effective way

What is evidence ?

Systematic Reviews of Randomized Controlled Trials (RCT)

- Gudmundur Skarphedinsson presentation of SRs
- An important asset for regulatory boards (e.g. The Swedish National Board of Health and Welfare/Socialstyrelsen)
- Minimizes work needed when working on clinical guidelines (just update)
- Estimate the risk of hidden trials statistically
- Bias tool gives an overview of the quality of the research field
- Summary statistics are more reliable than single RCTs
- Network SRs (still under trial) may revolutionize the field
  - Comparisons between all Txs,also methods not studied head-head
  - Mathematical model factors out level of placebo response/psychological unspecific factors ….
  - Liable to same faults as SR (cf. Cipriani (2017)) see Walkup (2017) for a discussion.

Walkup (2017) American Journal of Psychiatry **174**(5): 430-437.

To use resources in the most effective way

Why is evidence important?

Advantages and Limitations?

- If we carefully follow the evidence – as outlined - patients receive treatments that work
- Benefit has been carefully weighed against potential harm
- Treatment methods have been described in a way that makes it possible to apply them in a clinical context
- New leads, often described positively in the first report may be less effective during the replication process
- Many procedures used in clinical practise are difficult to include in a RCT but may still be important
  - Short waiting time, and good routines for diagnostic work-up that does not delay treatment
  - Information on treatment and advice on how to handle the symptoms & situation (cf. Goodyer, 2017 and Kendall, 2008)

Goodyer (2017) Lancet Psychiatry **4**(2): 109-119; Kendall (2008) Journal of Consulting and Clinical Psychology **76**(2): 282-297.

To use resources in the most effective way

Why is evidence important?

Using complementary evidence: I

Efficacy studies need to be seen in a wider context

- In CAMS: all treated with CBT, sertraline and COMBO improved vs PBO
- Moderator/predictor analysis: do some patients benefit more and others less on a treatment?
- personalized treatment

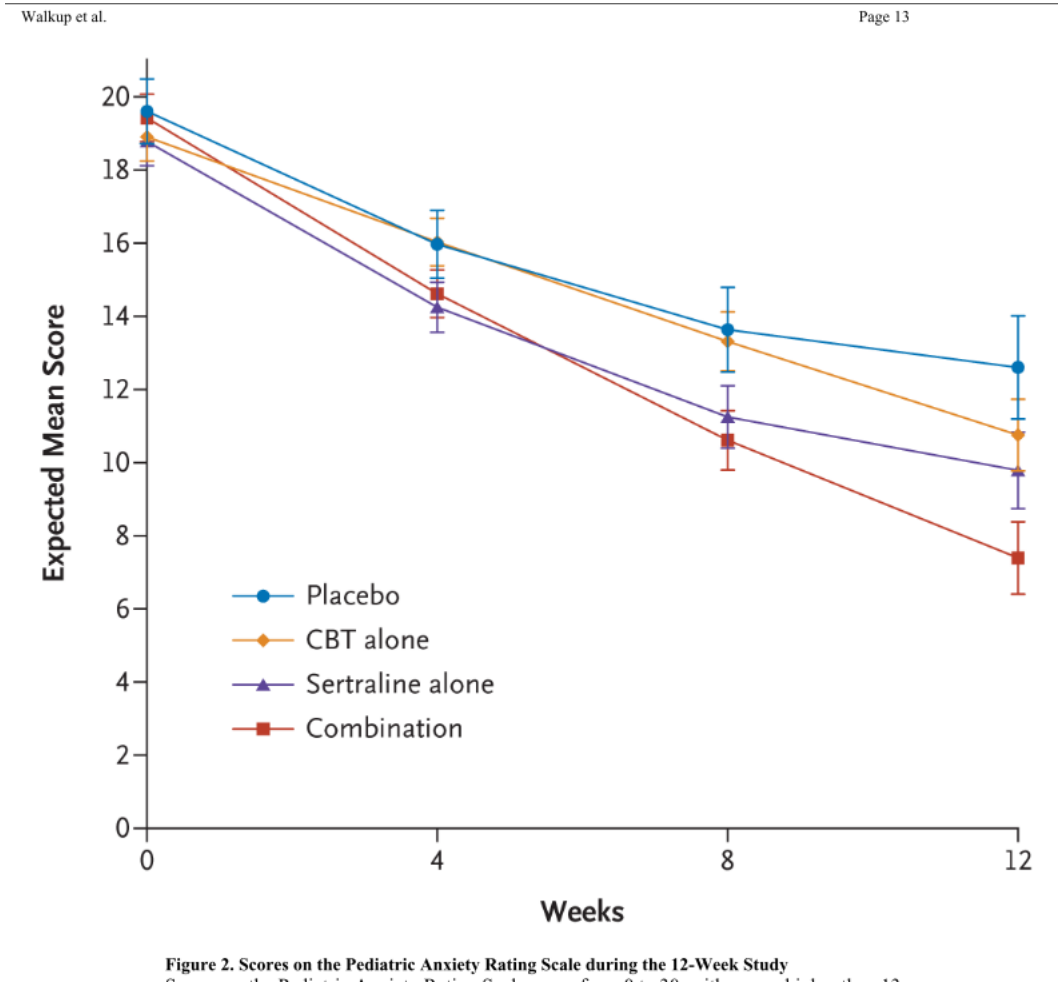


Figure 2. Scores on the Pediatric Anxiety Rating Scale during the 12-Week Study

Walkup (2008) New England Journal of Medicine **359**(26): 2753-2766.

To use resources in the most effective way

Why is evidence important?

Using complementary evidence: I

Efficacy studies in context

In CAMS: Moderator /predictor analysis: do some patients benefit more and others less ?

personalized treatment

Table 4

Child/Adolescent Anxiety Multimodal Study Moderator of Week 12 Treatment Outcomes—PARS Pairwise Effect Size Difference [95% Confidence Interval][a]

Moderator: Primary anxiety disorder subgroup	Treatment comparison												F (p value)[b]
	COMB vs. SRT		COMB vs. CBT		COMB vs. PBO		SRT vs. CBT		SRT vs. PBO		CBT vs. PBO		
	ES	95% CI	ES	95% CI	ES	95% CI	ES	95% CI	ES	95% CI	ES	95% CI	
SAD	−0.98	[−1.40, −0.55]	−0.91	[−1.31, −0.51]	−1.04	[−1.53, −0.55]	0.07	[−0.32, 0.46]	−0.06	[−0.53, 0.40]	−0.13	[−0.58, 0.32]	2.48 (0.04)
SoP	−0.16	[−0.48, 0.16]	−0.44	[−0.73, −0.16]	−0.59	[−1.02, −0.16]	−0.28	[−0.59, 0.02]	−0.43	[−0.87, 0.01]	−0.15	[−0.57, 0.28]	
GAD	−0.69	[−0.96, −0.42]	−0.48	[−0.76, −0.19]	−1.06	[−1.40, −0.72]	0.21	[−0.09, 0.51]	−0.37	[−0.72, −0.02]	−0.58	[−0.94, −0.22]	

Note. PARS = Pediatric Anxiety Rating Scale; COMB = combination of sertraline (SRT) and cognitive behavioral therapy (CBT); PBO = medication management with pill placebo; ES = effect size; CI = confidence interval; SAD = separation anxiety disorder; SoP = social phobia; GAD = generalized anxiety disorder.

[a] The standardized ES estimate, along with the 95% CI, is reported for each between-group pairwise comparisons. A standard ES estimate is defined as the average between treatment groups difference in the 12-month outcome scaled by the standard deviation of the outcome. Values of 0.2, 0.5, or 0.8 are generally regarded as small, medium, or large, respectively (Cohen, 1988). [b] This is a model-based omnibus test of the null hypothesis of no treatment effect moderation; that is, it is a test of the null hypothesis that for all pairwise comparisons simultaneously, the average between treatment groups difference do not differ by level of the moderator.

Anxiety disorders in CAMS: different response to the three treatment modalities

SAD: COMB > SRT = CBT = PBO

SoP: COMB = SRT > CBT = PBO

GAD: COMB > CBT > SRT > PBO

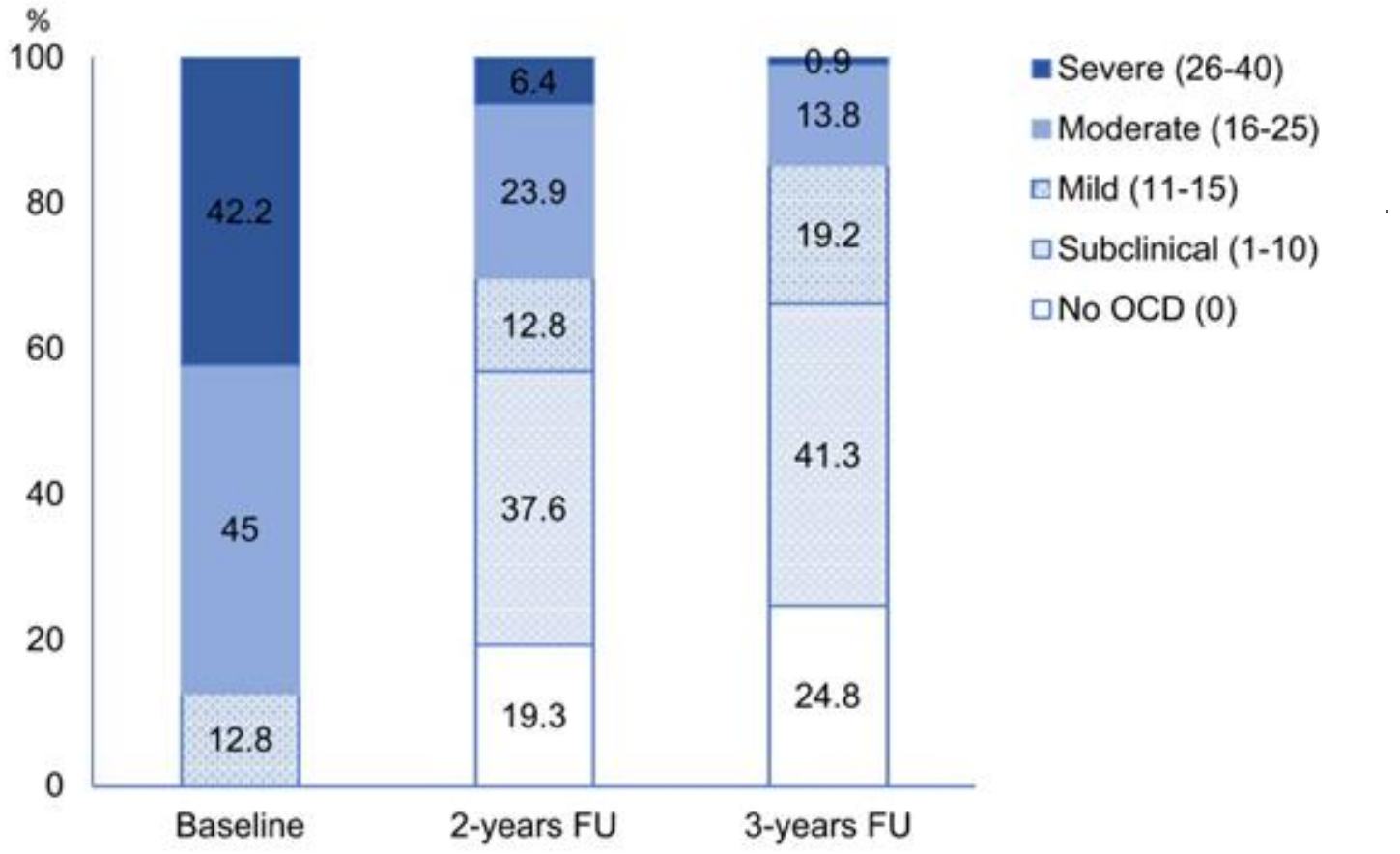
Other factors may predict outcome but do not show which treatment works best: severity, impairment, well functioning families etc …

Compton (2014) Journal of Consulting and Clinical Psychology **82**(2): 212-224.

To use resources in the most effective way

What is evidence ?

Using complementary evidence: II Effectiveness & naturalistic studies



- Using the March (1997) guidelines
- A "fixed window" follow-up scheme using independent evaluators
- Access to state of the art CBT and SSRI treament works

*March (1997) Journal of Clinical Psychiatry **58 Suppl 4**: 2-72; ^Skarphedinsson (2015) Nordic journal of psychiatry **69**(2): 81-92; ^Ivarsson (2015) Psychiatry Research **227**(1): 93–103; Melin (2018) JAACAP under review; Melin (2018) European Child and Adolescent Psychiatry **27**(10): 1373-1381.

Figure 3

To use resources in the most effective way

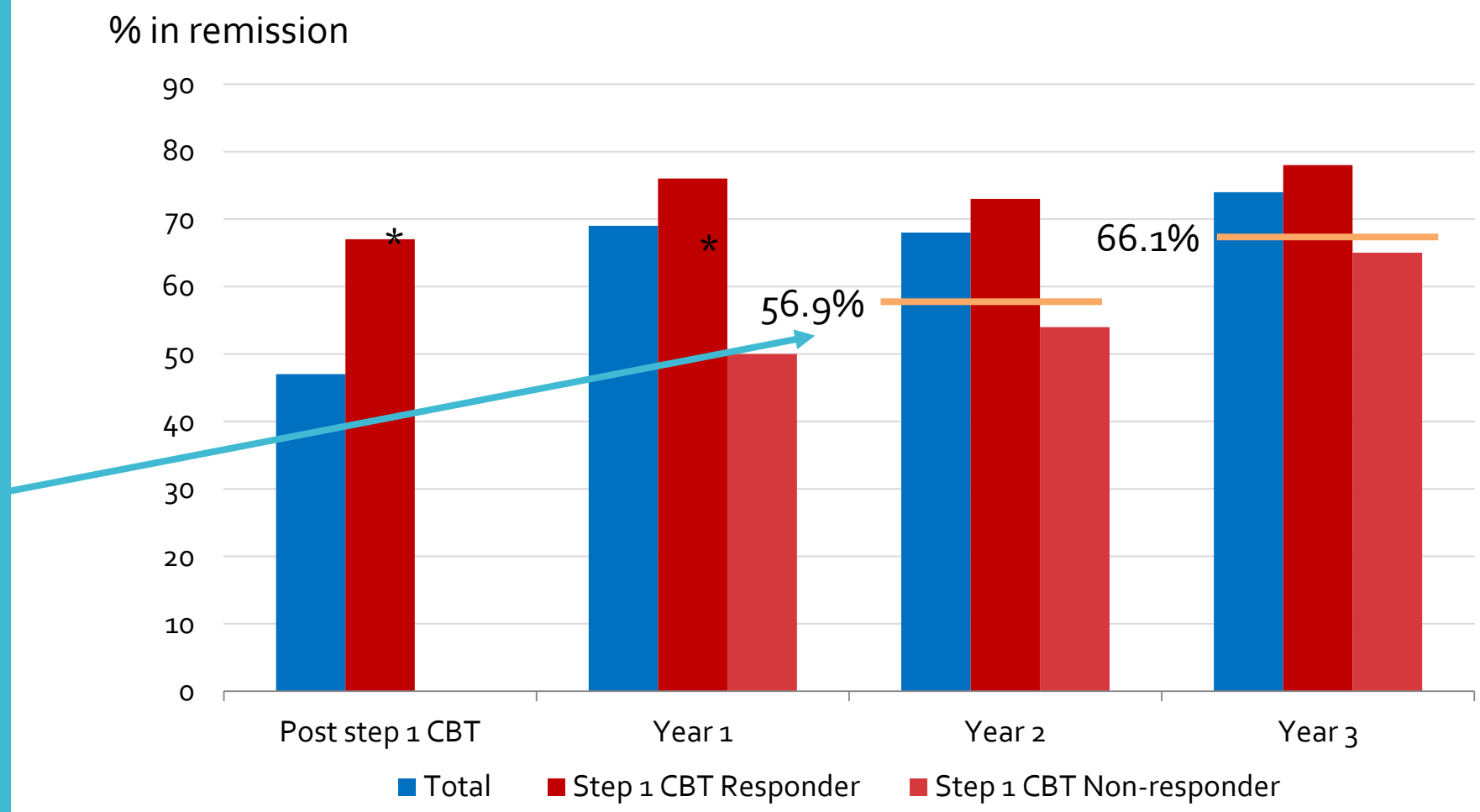
What is evidence ?

Using complementary evidence: II Effectiveness & naturalistic studies

'NordLOTS stepwise treatment study: remission versus the GBG 5 year cohort (Orange line)

Remission rates are lower but not markedly so

Using clinical guidelines: 1/CBT; SSRI+CBT or SSRI only leads to substantial benefit



To use resources in the most effective way

Setting priority

- What principles to use to set priorities for treatments?
  - The same disorder has several effective treatments
  - Different disorder have treatments of different effectiveness varying from very effective to little effect
  - Different disorders have different severity:
    - Life threatening (catatonia, severe treatment resistant depression with severe suicidality)
    - Severe-moderate (marked suffering, impairment and low QoL)
    - Mild disorder (some suffering and impairment but has still meaningfull relationships and QoL is not seriously low)
  - The cost/use of resources
- Society needs to decide what has highest vs lowest priority and to decide what should be used and not used in the clinics
- Hospitals/clinics need to decide how to implement society's needs/directions

http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19201/2013-9-17.pdf

Summary & Take Home message

To use resources in the most effective way

What is evidence ?

- Child- & adolescent psychiatry (CAP) has proven diagnostic methods available: if patients are to benefit from evidence based treatments good quality diagnostic procedures are necessary
- Evidence based child psychiatry is possible when care is based on empirical research as what we expect in medicine in general
  - Gudmundur Skarphedinsson will in the coming lecture decribe RCT and later systematic reviews of RCT in detail
  - Through understanding the evidence it is possible to understand its strengths and its limitations
  - Evidence need to be set in context when used with individual patients.
  - OCD as an example shows how different types of studies can be used to handle uncertainties based on experimental studies (RCTs)
- In the coming lecture I will discuss how the Swedish National Board of Health and Welfare works to provide clinical guidelines to aid hospitals and funding agencies in what treatments should be available and how to prioritize them.