Christopher Gillberg Evidence-Based Interventions in Child Neurosychiatry



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 - Stockholm, March 2016

Are autism, ADHD, and other child neuropsychiatric disorders "responsible" for the bulk of child and adult psychiatry? If so, can and should they be "treated"?

- GNC has more than 850 publications at PubMed, and another 200 publications in other data-bases, not PubMed; 31 books, of which 14 published in the US/UK (translated into 12 languages), and CG is on Thomson Reuter list of 3000 most cited researchers in the world (any field), 3 most cited in medical field in Sweden
- The GNC has been active in developing and researching 3 muchused diagnostic tests (ASDI, DISCO, PDMR), 5 internationally leading screening tools for autism/ADHD/neuropsychiatry (ASSQ, FTF, A-TAC, BCSQ, ASDASQ), and in evaluating several "new" interventions in RCTs, open label trials and naturalistic studies

Focus of study at GNC: Early Symptomatic Syndromes Eliciting Neuropsychiatric/Neurodevelopmental Clinical Examinations (ESSENCE)

Syndromes

- Autism (Autism Spectrum Conditions, including Disorders)
- ADHD (Attention-Deficit/Hyperactivity Disorder) with or without ODD/CD (Oppositional Defiant Disorder/Conduct Disorder)
- SLI/LI ("Specific" Language Impairment)
- LD/MR (Learning Disability/Mental Retardation), NVLD (Non-Verbal Learning Disability), Working Memory Disorder, and Slow Processing Disorder - with psychiatric problems
- Anorexia nervosa and other eating disorders
- TS (Tic Syndromes including Tourette Syndrome)
- DCD (Developmental Coordination Disorder)
- BPS (Behavioural Phenotype Syndromes)
- Epilepsy Syndromes including Landau-Kleffner Syndrome
- PANS

EBM

• Evidens innebär "bästa tillgängliga vetenskapliga bevis. Att arbeta med EBM innebär att kombinera evidens med kliniskt kunnande och patientens unika situation och önskemål". (SBU)

• Vad är evidensbaserad medicin?

 "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research...External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision." (Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ, 1996, 13, 71-72)

Vetenskap och beprövad erfarenhet

- I HSL 1982 och Förordning med instruktion för Socialstyrelsen (2015) används genomgående begreppet **"vetenskap och beprövad erfarenhet"**
- Men vad är det?
- **PRIMUM NON NOCERE (Hippokrates eller Sydenham?)**

General points when interpreting published results

- **Financial conflicts of interest** are very important in interpreting published work
- Published work where authors have financial interests tend to show positive results
- Published work with robust study designs and without authorial financial interests tends to show no effects (for example in the case of Triple P (Wilson et al., 2012) and more recently the Family Nurse Partership (Robling et al.))
- There are occasional exceptions: for example the Incredible Years programme has had several independent trials demonstrating effectiveness
- Financial interests are often not declared by authors, with some authors being much less disclosive than others. (Eisner, Humphreys, Wilson, & Gardner, 2015)
- CAVEAT EMPTOR!
- Wilson, P., Rush, R., Hussey, S., Puckering, C., Sim, F., Allely, C., . . . Gillberg, C. (2012). How evidence-based is an 'evidence-based parenting program'? A PRISMA systematic review and meta-analysis of Triple P. *BMC Medicine*, *10*(1), 130. Retrieved from
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- Eisner, M., Humphreys, D., Wilson, P., & Gardner, F. (2015). Disclosure of financial conflicts of interests in interventions to improve child psychosocial health: A cross-sectional study. *PLoS ONE*, *10*(11), e0142803. doi:10.1371/journal.pone.0142803

Interventions for autism

• Early intensive and non-intensive behavioural therapies/learning

- Weak-no evidence for any long-term effects
- Strong evidence for highly variable outcomes regardless of intervention (with IQ, language, medical disorders (and ADHD?) being the strongest predictors)
- Some evidence for better outcomes in individuals with autism and IQ>70
- Some evidence for effects lasting 2-24 months
- Three largest (including two naturalistic) studies do not indicate differences across those who received very intensive interventions and those who received parent training and non-intensive interventions for a few years
- Some indications that lack of regular follow-up is associated with adaptive functioning decline in 6-10-year perspective
- Indirect indications that stress reduction can lead to decrease in schizophrenia/psychosis trajectory/outcome
 - Howlin et al 2009, Darrou et al 2010, Fernell et al 2011, Unenge-Hallerbäck et al 2012, Reichow et al 2012, Oono et al 2013, Fernell et al 2014, Gillberg and Fernell 2014, Barnevik Olsson et al 2016, Waterhouse et al 2016

Interventions for autism

- Supplements
 - Vitamin D low in autism newborns, children, adults and in mothers of children with autism, D-suppl reduces risk?
- Exercise
 - Systematic review provides weak evidence of moderate effect size for martial arts, yoga, horseback-riding etc
- Medications
 - Bumetanide: one study showed moderate effects on CARSscores, including over several months
 - Oxytocin: equivocal results, no long-term studies
 - Melatonin: beneficial in short term for sleep
 - Risperidone and aripiprazole: good evidence in terms of reducing irritability, but many side effects, not effective for "autism"
- Diagnosis
 - Early diagnosis and early information can possibly (in themselves) improve outcome

Nydén et al 2008, Lemonnier et al 2012, Westman Andersson 2013, Unenge Hallerbäck et al 2012, Schwichtenberg and Malov 2015, Fung et al 2016, Accordino et al 2016, Sacrey et al 2015, Fernell et al 2015, Bremer et al 2016, Stubbs et al 2016

Interventions for ADHD/attention deficits/impulsivity

• Medication/stimulants

Overwhelming and very strong evidence (with effect sizes from 0.7-1.8) that central stimulants are effective in the treatment of attention deficits and impulsivity whether in children with a diagnosis of ADHD, ADHD combined with other disorders/symptoms, or attention deficits only; one placebo-controlled 12-18-month follow-up study showing persisting positive effects; register studies suggest protective effects on accidents and criminality

Medications/non-stimulant

- Moderate effect-sizes for positive (including several years?) effects of atomoxetine
- Weak to moderate effect-sizes for some other medications, including guanfacine
- Medications/supplementations
 - Weak to moderate evidence that subgroup with ADHD benefits from supplementation with Omega-3

Gillberg et al 1997, Johnson et al 2009, McDonagh et al 2011, Ginsberg and Lindfors 2012, Konstenius et al 2014, Chang et al 2014, Biederman 2016, Stevenson et al 2014, Buoli et al 2016, Michelsen et al 2016 in progress

Interventions for ADHD/attention deficits/impulsivity

- Working memory training
 - Weak and conflicting evidence of moderate effect on working memory deficits in ADHD
- Martial arts and yoga
 - Weak evidence that there is moderate effect size for EF

Klingberg et al 2005, Diamond and Lee 2011, Strayhorn and Strayhorn 2011, Cortese et al 2015,

Interventions for conduct disorder and ODD

- Many parenting interventions claim effectiveness in reducing child disruptive behaviour (including Triple-P and CPS)
- Some of them probably are effective, but:
- Generally, published studies claiming success have (Wilson et al., 2012):
 - Sample sizes that are too small
 - Multiple outcome measures and no principal outcome pre-specified
 - No active control group (waiting list control conditions usually cause deterioration so are not a fair comparison)
 - Well-educated volunteer samples
 - No independent assessment of child behaviour
 - Authors with financial conflicts of interest
- Wilson, P., Rush, R., Hussey, S., Puckering, C., Sim, F., Allely, C., . . . Gillberg, C. (2012). How evidence-based is an 'evidence-based parenting program'? A PRISMA systematic review and meta-analysis of Triple P. *BMC Medicine*, *10*(1), 130. Retrieved from <u>http://www.biomedcentral.com/1741-7015/10/130</u>

Interventions for Tourette syndrome

- Good evidence that anitpsychotics are effective in the short-term treatment of tics, but risk of side effects high
- Good evidence that there is a moderate effect (0.6) on tics (and associated "OCD-features") of using a variety of Habit Reversal Training Programmes

Hollis et al 2016

New trends in neuropsychiatry research - the future

- The overlap with "everything and anything" will become widely recognized and lead to comprehensive, not over-focused, assessments, never forget height, weight, OFC, vision, and hearing
- More and more of "ESSENCE" will be defined by their etiology (cf Rett syndrome, 22q11, SCN1A, PTEN1, and Fragile X to mention but a few)
- Functional impairments will be related to neuropsychological constructs (NVLD, working memory disorder, slow processing disorder etc.)
- Girls will be recognized as having neuropsychiatric disorders much more often than is currently the case
- Education about ESSENCE at all levels (specialists and general public, teachers and children in schools etc.) will probably lead to better QOL
- Psychoeducation, parent training, "insight" and physical activity
- Cognitive training programmes will become more specific
- Medication for some symptoms but not for disorders, e.g. stimulants for attention deficits, melatonin for sleep, omega-3, vitamin D, antiinflammatory medications, diets
- Intervention makes a difference: how and when?
- Quality of life better than previously believed?