Challenges and controversies in the treatment of adolescent major depression

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declarations of interest: none

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Outline

- Some challenging facts about adolescent depression
- Antidepressants: controversies
- Guidelines: UK vs US
- Combined treatment trials
- Treatment resistant depression
- SSRI suicidality controversy
- Psychological treatment challenges
- Future research
- UK IMPACT study
Scores for the Center for Epidemiologic Studies Depression Total Scale and 3 Subscales Across Adulthood

Estimated trajectory of scores for the Center for Epidemiologic Studies Depression (CES-D) total scale and 3 subscales across adulthood. Raw scores were z-transformed so that all scales could be plotted on the same axis. (eFigure 1 in the Supplement shows the estimated trajectories of each scale in the original metric.)
Prevalence Adolescent MD

US National Comorbidity Survey
Avenevoli JAACAP, 2015

- Lifetime 11.0%; severe MD 3.0%
- Increases across adolescence, females > males
- Severe MD: 2-5x greater comorbidity & impairment, suicidality++
- Minority receive specialised treatment
- NB sub-threshold MD: ~30% in European adolescents, predicts impairment & suicidality (Balazs JCPP 2013)
Increase in prevalence of emotional problems over 20 yrs in England
Collishaw, JCPP, Aug 2010

% frequently anxious/depressed

English national cohort study
OR:
boys 1.84
girls 2.40
Secular changes mood disorders
review Collishaw JCCP March 2015

High income countries

- Increased service use
- Cross-cohort comparisons show increase over 30 yrs, eg Norway, UK
- Recent increase in young male suicides

Causes?

Poor sleep, changes in personality traits (Twenge 2011), increase in parental depression, cyber-bullying, academic demands, social inequality, recession
Juvenile vs adult onset depression: more severe

STARD study, Zisook, AJP, 2007

- N 4,0041, 18-75 years

- Juvenile onset associated with more impairment, comorbidity, high recurrence, severity, suicidality, substance abuse
COMORBIDITY IN CLINICAL SAMPLES in UK: ADAPT
(Goodyer, Dubicka et al, BMJ, 2007)

89% comorbid for at least 1 other disorder

N 208

cf ESMcD community study
2004
53% comorbidity in adult MD
High rate of recurrence and chronicity

- TADS: 96% recover by 42 months, but only half depression free during FU (Curry AGP 2011)
- Adolescent onset recurrent MD = severe group, impairment into adulthood (Wilson Psychol Med 2015)
- Risk factors: life events, Hx minor depression, female, family Hx recurrent MD, borderline personality symptoms (girls) (Oregon Adolescent Depression Study Rohde 2013)
Depression important risk factor for suicidality

GSMS, Foley et al, AGP, 2006
SUICIDALITY and COMORBIDITY

GSMS, Foley et al, AGP, 2006

ADAPT study:
Conduct disorder increased risk
Antidepressants
UK National Institute Clinical Excellence (NICE) guidelines

NICE 2005

Do not use ADs in mild depression

Specialist psychological treatment always first line

Specialist psychological treatment needs to be given with ADs: protective effect

NICE evidence update 2013

Limited benefits of combined treatment, including for suicidality
Can now consider fluoxetine for initial treatment

ADs must only be given with psychological therapy (not specialist)

Specific psychological therapy for 3/12 (CBT, IPT, FT, PPT)
#### UK and US guidelines and licensing in C&A depression

Dubicka et al, Clinical Topics in C&A Psychiatry, Royal College Psychiatrists, 2014

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UK “no/low/slow” vs US “go/go/go”

~1.5% UK 13–18 yr olds taking ADs (before warnings)
3.7% US 12–17 yr olds (2005-2008 post warnings)

- ?best outcomes
- ?which more cost-effective
- Data driven, so why differ?
Newer generation antidepressants: some issues with placebo controlled trials

- Differing methods
- Age range 6-18
- Severe, complex, suicidal cases excluded
- Most US drug industry sponsored
- Previous unpublished negative data

(Reyes, JACAAP 2011)
Efficacy newer generation antidepressants: meta-analyses

Hetrick, Cochrane Review
SSRIs RR 1.28; fluoxetine 1.86 (2007)

adolescents: only flx and escitalopram show consistent evidence of efficacy for >1 outcome (2012)
Efficacy meta-analysis: risk differences for different indications
Bridge et al, JAMA, 2007

20% difference for fluoxetine
Relapse prevention
Cochrane, Cox, 2012

3 trials

% relapse

- antidepressant
- placebo
Review (select) of meta-analyses of medication efficacy in psychiatry and general medicine Leucht BJP 2012
Adverse effects
Safety in overdose
Hawton et al, BJP, 2010
Adverse effects

Liver abnormalities (Voican AJP 2014)
- Up to 1% SSRI/NSRIs, idiosyncratic

Neuroendocrine (Jerrell, CNS Neurosc, 2010)
- e.g. Weight gain OR 1.49
- Least weight gain with fluoxetine (Blumenthal JAMA 2014)

Risk of (hypo)mania (Offidani, Psychotherapy & Psychosomatics 2013)
- 8.19% vs 0.17% in placebo
Risk of agitation or hostility
Hammad 2004, FDA

Meta-analysis 2013, Offidani: RR 1.7 for activation
Evidence base for combined treatment (SSRI+CBT)

Is it more effective and cost-effective than a single treatment?

Does specialist psychological treatment confer a protective effect to antidepressants (NICE 2005)?
Meta-analysis of combined treatment: only short-term benefit for impairment

Dubicka et al, Dec 2010, BJP
TADS: Depressive symptoms (CDRS) at 12 weeks
(March et al, JAMA, 2004)

Comb vs flx p 0.02
Not significant for CGI.
Flx vs CBT p 0.01

NB no advantage of comb in more severe cases
TADS study: effect sizes for CDRS-R
March et al, JAACAP, 2006

NB severity analysis showed no superiority of COMB over FLX in most severe cases or for impairment; No difference at 36wk
TADS suicidality: some protective effect
Emslie et al, JAACAP, 2006; AGP, 2007

- 12 wks: no significant differences for suicidal ideation

- 36 wks naturalistic FU: significantly higher suicidal ideation with FO vs COMB: 8/55 14.5% vs 0/63 (2/53 CBT)
ADAPT: Goodyer, Dubicka et al, BMJ, 2007

Quality of life (HoNOSCA)
SSRI+CBT+TAU vs SSRI+TAU

Average treatment effect = 0.001, $p = 1.0$

No effect on any outcome; not cost-effective

~20% depression resolved with a brief initial intervention
ADAPT: Suicidal ideation

Average treatment effect: 0.91 (0.39 to 2.11), p 0.82
TORDIA: SSRI-resistant adolescent depression
Brent et al, JAMA, 2008
Improvement (CGI-I) at 12 weeks

% improved much/very much

no CBT vs CBT p 0.04, not for depression
SSRI vs venlafaxine p 0.44
TORDIA harm-related events at 12 weeks

NB more serious adverse events in CBT arm at 24 wks (4.5% vs 0.7%, p = 0.06)

More CV and skin problems with venlafaxine
TORDIA suicidal ideation

No sig diffs
Role for combined treatment
Dubicka & Brent, Int JCog Therapy, 2014

- Treatment resistance – increased emphasis on activation (TORDIA)
- Comorbidity
- High levels of cognitive distortions
- But less effective if Hx abuse
CBT for relapse prevention
Kennard AJP 2014

- 144 C&A who responded to fluoxetine
- Flx vs flx+CBT for 30wks
- Lower risk of relapse with CBT: 9% vs 26.5%
- No difference for remission
Treatment resistance

ADAPT: predictors of end-point depression (Wilkinson et al, BJP, 2009)

- Severity
  (Clarke ‘92; Asarnow ‘09, TORDIA)
- OCD
- Suicidality (trend, p=0.054)
  (Tordia, Asarnow ‘09)
- Disappointing life events
Other predictors of non-response

- Sub-syndromal bipolar symptoms (TORDIA, Maalouf JAD 2012; Li BJP 2012)

- Family conflict (Birmaher AGP 2000; Rengasamy 2013)

- Substance abuse (Goldstein TORDIA JACAAP 2009)

- Childhood maltreatment -> poor response in adult trials (Nanni AJP 2012)
Insomnia

- poorer response to flx: 39 vs 66% (Emslie 2012)
- predicts MD in community samples (also ODD, anxiety) (Roberts, JAD, 2013; Shanahan JAACAP 2014)
- Meta-analysis: decreased sleep in C&A over past 100 yrs (Matricciani Sleep Med Reviews 16 2012)
- Delayed sleep onset 2x more common in depressed youths vs controls; assoc with smoking, short sleep duration, chronic psychological ill health (Glozier Bmc Psych 2014)
Treat parents

- IPT for depressed mothers (vs TAU) -> significantly less depression in offspring at 9/12
  (Swartz AJP 2008)

- Maternal SA increased offspring's risk of self-harm with suicidal intent and of suicidal thoughts (not NSSI)
  (Alspac, Gunnell JAACAP 2014; also Brent JAMA 2015)
Treatment Resistant Depression: management

- Meta-analysis of meds strategies, eg Li n411, 8 studies, most small (2 RCTs)
- Response for active treatments: 46% (Zhou 2014 BMC Psych Review)
- Other psychological treatments, eg BA if anhedonia, mentalizing/DBT if NSSI (Dubicka, IJCT, 2014)
- ECT: rarely used, case reports only (Grover, Journal ECT, 2013)
Suicidality risk with SSRIs: RCT data

- Overall, small effects e.g. 4.8 vs 3.0% (Dubicka et al 2006 BJP)

But:
- Trials problematic; exclude most impaired and suicidal

- Some consensus of greater efficacy and safety of fluoxetine (e.g. CSM 2003, Whittington 2004, NICE 2004, Cheung 2005, ACNP 2006)
In youths and young adults, no significant differences between drugs or diagnoses.
Other evidence

- No evidence for *increase* in suicides with increased prescribing worldwide (Baldessarini, HJP, 2007; Wheeler, BMJ, 2008)

- Large European study of 29 countries (1980 - 2009):

  Suicide rates have decreased more in countries with greater use of Ads (except Portugal) (Gusmao, PLOS, 2013)
Other evidence cont

- Less attempts if treated with ADs and with longer term treatment (6 months) (Valuck, CNS drugs, 2004; Gibbons, AJP 2007)

- Decreased risk of suicide and death with ADs (Tiihonen, AGP, 2006)

- ADs rarely detected in suicide autopsies (eg Cortes 2011)

- Adolescent suicides: only 1.6% exposed to ADs (Dudley 2010)

But: Review of MD observational studies
SSRIs associated with increased attempts and suicide in adolescents, not adults (Barbui, CMAJ, 2009)
Attempts in adolescents and young adults before and after starting antidepressants or psychotherapy: Simon, AJP, 2007

Attempts highest in month before treatment
Depression and suicide

- Depression most common diagnosis in autopsy studies of suicide (Shaffer 1996)

- Utah Youth Suicide Study: untreated mental illness due to reluctance to seek help implicated in suicides, rather than adverse effects of receiving treatment (Moskos, SLTB, 2007)
UK youth suicide data and diagnosis 1997-2003
Windfur, JCPP, 2008

NB only 8% suicides prescribed SSRIs, but affective disorder leading cause of death cf Isacsson & Ahlner, Sweden (2014) - increase in suicides in untreated youths post warnings
So are the SSRIs safe and clinically effective??

Assess in each case

*Increased severity, greater risks from depression* -> *increased potential benefit, and reduced risk*

*However decision complex*

*Involves individual beliefs and cultural expectations*

*Informed personal choice*

*‘guidelines vs rules’ (Murphy 2014 HRP)*
Issues in evidence base for psychological treatment: ‘uncritical positive regard’
Nutt JPP 2008

- quality of studies
- non-active controls
- publication bias
- not blinded (expectancy effect)
- no measurement of adverse effects
- less stringently monitored

Parker BJP 2009

‘if psychotherapy is powerful enough to do good, it may be powerful enough to do harm’

Dimidjian & Hollon, Amer Psychol 2010
Adult data: meta-analyses psychological treatment studies in depression (Cuijpers, Psychol Med & BJP, 2010)

Overall studies poor quality
Thoma, AJP, 2012
Meta-analysis: psychological treatment in C&A depression

Weisz et al, Psychol Bull, 2006

- N 31 CBT studies
- N 13 non CBT studies
- Treatment effects lost in long-term
Other psychological treatment

**IPT**
- 3 RCTs with positive results (ES 0.45)  
  (Mufson 1999, 2004)

**Family therapy**
- trials with active controls negative; evidence for family psychoeducation  
  (Harrington 1998; Clarke 1999; Brent 1997; Fristad, AGP, 2009)

**Psychodynamic therapy**
- Meta-analysis C&A disorders (n11); no difference  
  (Abbass, JAACAP 2013)
Potential targets for treatment

- **Co-Rumination:** MD youth co-ruminate more & problem-solve less with peers vs healthy youth; also co-ruminate with parents (Waller, JAACAP, 2015)

- **Exercise:** meta-analysis - limited evidence that exercise improves depressive symptoms vs control IV (Rimer, Cochrane, 2012)

- Longitudinal adult cohort study, activity
  - less symptoms from 23-50 years (Pereira, JAMA Psychiatry, 2014)
Inflammation

- Population longitudinal study (ALSPAC): children aged 9 with higher interleukin-6 values were more likely to be depressed at 18 years (adj OR 1.55); also psychosis (Khandaker, JAMA Psych, 2014)

- Meta-analysis: n 14 RCTs, anti-inflammatory treatment reduced depressive symptoms (SMD −0.34) vs placebo (Köhler, JAMA Psychiatry, 2014)
Pharmacogenetics

Rotberg et al JCAPP 2013

- Serotonin pathway polymorphisms
- N83 C&A with anx/dep
- Citalopram treatment
- Long allele of serotonin transporter and G allele of tryptophan hydroxylase 2 -> 80% response
- Vs 31% response with short and T alleles
Public health interventions: smoking

- Blood cadmium in young adults assoc with depressive symptoms in non-smokers (OR 2.91) & current smokers (OR 2.69) (Scinicariello Psych Med 2015)
Specialist Clinical Care for all cases ($N = 510$)
Relapse prevention study
6/12 acute treatment, 18/12 follow-up

Manchester (Hill, Dubicka), Cambridge (Goodyer, Kelvin),
East Anglia (Reynolds), UCL (Fonagy, Target, Senior)
Specialist clinical care manual (SCC)

- Formulation
- Psychoeducation
- Optimistic reassurance and convey expertise
- Realistic expectations
- Manage context: identify and address risks
- Monitor mental state and suicide risk
- Liaison with school, etc
- Family work
- ‘Emotional first aid’, e.g. sleep hygiene, behavioural activation, praise, problem solving, expressing thoughts and feelings

(Goodyer, Dubicka et al, BMJ, 2007; Kelvin, Dubicka et al, IMPACT study)
Conclusions

Simple interventions first:
Routine CAMHS care may help in 20% MD (ADAPT)

Often complex: one treatment unlikely to have large effect

Informed choice

Antidepressants: for more severe cases; assess risk/benefit; always with psychosocial treatment

Specialist psychological interventions in milder cases, if SSRI alone not effective, and CBT for relapse prevention - await IMPACT results

Ongoing challenges, limited evidence base but promising new directions
Thank you

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