

This draft has a conditional acceptance from the JCCP – Please do not copy, use, quote or replicate in any form without the express permission of the authors

Practitioner Review: Therapeutics of Unipolar Major Depressions in Adolescents

Paul O Wilkinson and Ian M Goodyer

Developmental Psychiatry, Department of Psychiatry

University of Cambridge Clinical School

Address for Correspondence:

Douglas House, 18b Trumpington Road, Cambridge CB2 8AH

Corresponding Author: ig104@cam.ac.uk

Declarations of Interest

Both authors consult to Lundbeck on randomised control studies of depressed children and adolescents.

POW has consulted to Takeda.

POW is an interpersonal psychotherapy supervisor and trainer.

Background: Over the past 2 decades new and key randomised controlled trials have reported the efficacy, clinical and cost effectiveness of psychological and pharmacological treatments for adolescents with major depression.

Methods The literature was searched through pubmed, psychinfo , scopus and web of science for randomised controlled trials of current major depression together with meta-analyses and systematic reviews of trials between 2000-2017. Those specific to the adolescent years (11-18 years) were taken as the primary source for this narrative review. Additional selected studies in adults were used to illustrate methodological issues.

Results: Manualised psychological therapies and the SSRI fluoxetine are more effective than active placebo in the treatment of major depressions. Mild to moderate illnesses attending community-based services are likely to benefit from psychological treatment alone. Moderately to severely ill patients attending clinic and hospital services are likely to benefit from monotherapies or combining psychological and pharmacological treatment. Antidepressants carry a small but significant side-effect risk including increased suicidality. Side effects from psychotherapies are somewhat lower but specific negative consequences remain less well characterised. There is some evidence that CBT-based approaches prevent onset of major depression episode in well adolescents at high-risk. Other psychological interventions have not been adequately studied. There has been only limited identification of treatment moderators and no clear understanding of therapeutic mechanisms.

Conclusions: There is now a range of clinically-effective treatments for depressed adolescents. Future research needs to reveal moderators of and mechanisms for individual differences to treatment response, determine psychotherapies of value for milder depressions, enhance our understanding of safety and side-effects for all treatments, and consider how to reduce and treat treatment-resistant cases.

Keywords depression, adolescents, psychotherapies, antidepressants

Introduction

This practitioner review considers the current state of knowledge regarding the treatment and prevention of major depressive episodes in adolescents.

Selection Criteria for studies used in this review

The literature was searched through pubmed, psychinfo, scopus and web of science for randomised controlled trials of current major depression and prevention of clinical depressions across the lifecourse together with meta-analyses and systematic reviews of trials of participants all between 2000-2017. Those specific and/or inclusive of the adolescent years (11-18 years) were taken as the primary source for this review. Additional studies in adults were used to illustrate methodological issues.

The studies used in this review fulfilled the following criteria:

Primary Treatment Studies:

- i) Adolescent patients with current interviewer-diagnosed DSM major depressive episode recruited into randomised controlled trials testing for treatment efficacy or effectiveness.
- OR
- Recruitment via self-reported depression symptoms or a history of affective disorder in parents into randomised controlled prevention trials.
- ii) Required a theory-based investigation with a declared a priori hypothesis that the nominated treatment of interest was superior (statistically and clinically significant) by end of study than the nominated control condition or no worse (not inferior to) than the nominated reference treatment.
 - iii) RCT studies were planned with sample size estimates with a power of at least 80% and an alpha of 5%, this representing the current accepted tolerance for a false positive result.

Reviews:

Metanalyses and systematic reviews where studies described the search method and data analytic strategy according to accepted guidelines.

As a result the major clinical scientific conclusions on treatment of a depressive episode are drawn from the 4 key randomised controlled trials reporting psychological and pharmacological treatments for depressed adolescents (March, Silva et al. 2004, Goodyer, Dubicka et al. 2007, Brent, Emslie et al. 2008, Goodyer, Reynolds et al. 2017).

In addition there are a set of studies on preventing the incident onset of major depression (Garber, Clarke et al. 2009 , Stallard, Sayal et al. 2012, Richardson, Ludman et al. 2014, Brent, Brunwasser et al. 2015). We also utilise results of 6 meta-analyses and systematic reviews (Hetrick, Cox et al. 2015, Cipriani, Zhou et al. 2016, Hetrick, Cox et al. 2016, Weersing, Jeffreys et al. 2017, Weisz, Kuppens et al. 2017, Werner-Seidler, Perry et al. 2017). The papers that are core to this review are described in tables one and two.

Tables one and two here

Designing Trials for studies of adolescent depression

Samples and selection criteria

Current patients have been recruited from hospitals, child and adolescent mental health clinics, independent practice, primary care settings and schools and directly from the population. Inclusion criteria varied between studies: for example, the Treatment of Adolescent Depression Study (TADS) study excluded acutely suicidal and psychotic patients at recruitment whereas the Adolescent Depression and Psychotherapy Trial (ADAPT) included such patients (March, Silva et al. 2004, Goodyer, Dubicka et al. 2007). Prevention or early intervention use schools and community clinics as recruitment sites. Cluster designs are preferred in which intact social units or clusters of individuals (eg school classes or year groups) are randomly allocated to intervention groups (Werner-Seidler, Perry et al. 2017).

Effect sizes and p values from RCTs

How best to understand trials results is not determined by the significance of results alone. A very large influence on the p value (conventionally taken as 0.05) reporting statistical significance is sample size; the p value is also affected by the choice of measures, design and analytic procedures (Kraemer and Blasey 2015). Failure to find a 'significant' p value may mean there is no true difference between treatments or that there is a difference but that the study was underpowered. It does not mean that there is definitely no difference.

From the therapeutic perspective, the effect size (ES) is perhaps a more useful statistic than the p value. When there are continuous results (such as final scores on a self-rating questionnaire) Cohen's d, also known as standardized mean difference, or the more conservative Hedges g is reported which gives the degree of overlap of the distributions

of the scores, with consensus-agreed thresholds to interpret it. An effect size reported for dichotomous results (such as recovered vs non-recovered) is the success rate difference (SRD – probability of recovered in the active treatment group minus probability recovered in the control group). The number needed to treat (NNT) equals $1/\text{SRD}$. The NNT answers the question: How many patients must be treated with an intervention to get one more recovered compared to if they are all given a control treatment? Too small a sample size is a major reason for statistically non-significant findings and a common flaw making many treatment studies uninterpretable. Combining small trial results and looking for effects through pooling data and conducting meta-analyses is one method for combating lack of sample size.

Placebo, nocebo and their effects in trials

There is growing evidence that 'placebo' has active effects expressed through psychological and neural changes (Kaptchuk and Miller 2015). Such effects may operate through expectancy and beliefs about therapy prior to or as a consequence of randomisation. The placebo response in the best designed trials across the lifecourse report active placebo rates of around 30%-35% (Walkup 2017). This implies that treatment response greater than 35% effectively consist of active placebo+ active treatment.

Less research has been devoted to the *nocebo effect*: when a negative expectation causes a control condition to have a more negative outcome than it otherwise would. In medicine overall it has been estimated that between 4 and 26% of patients who are randomly assigned to placebos in trials discontinue their use because of perceived adverse effects (Kaptchuk and Miller 2015). There have been no studies of the nocebo effect in treatment trials of depressed adolescents.

Are there effective treatments for depressed adolescents?

Psychological Therapies

Although early RCT reports of CBT and IPT (interpersonal psychotherapy) reported results in favour of the specialised treatment the standardised mean difference is now reported as around 0.29, a 'small' effect size when compared to their active control groups (Weisz, Kuppens et al. 2017). This may be due to a combination of improved methodological rigour and better active control treatments. A recent metanalysis does confirm however that both CBT and IPT are efficacious and clinically effective (Weersing, Jeffreys et al. 2017). The number (n=6) and small sample size of IPT studies

and that CBT effects may be attenuated in clinically complex samples warrant positive but cautious interpretation of results to date.

The IMPACT study (results of which were not included in the above meta-analyses) is the most recent pragmatic effectiveness trial. The study compared psychological treatments for depressed adolescents attending specialist UK NHS CAMHS clinics (Goodyer, Reynolds et al. 2017). Two theory driven specialist therapies, CBT and short term psychoanalytic therapy (STPP) were evaluated against a pragmatic reference treatment termed brief psychosocial intervention (BPI: described below). The study was sufficiently powered (n=465) to be the first to examine whether specialist therapies delivered by highly trained personnel would exert therapeutic gains over and above those expected from a relatively simple active approach delivered via a manual by psychiatrists and mental health nurses in CAMHS. The critical value of IMPACT was the demonstration that CBT was not superior to STPP and that surprisingly, all three psychological treatments were as clinically effective as each other by both end of treatment and at 12 months post treatment follow up. We did not plan to test for statistical equivalence of CBT or STPP with BPI, so we cannot infer that they are clinically equivalent for all patients. Further the absence of a placebo control group in the study means improvements during or post-treatment may be due in part or whole to time alone.

BPI for depressed adolescents: a brief outline

BPI used in IMPACT consisted of psychoeducation, action-oriented, goal-focused, and interpersonal activities but did not use cognitive or analytic techniques. The 3 core principles underpinning BPI are: i) a collaborative approach; ii) selected use of behavioural activation techniques iii) subsequent instigation of recovery support methods. For experienced mental health professionals BPI training is 1 day with a second day for reflection and clarification, plus ongoing supervisions in groups. The treatment duration was planned as up to eight individual sessions with up to 4 family sessions over 20 weeks. There is prior evidence that brief psychosocial interventions are efficacious for mild to moderate depression and anxiety disorders in both adolescents and adults (Klerman, Budman et al. 1987). The BPI method used in IMPACT needs replication and testing in the community to determine its value in non-clinic settings.

Attachment-Based Family Therapy

Traditional structural systemic family therapy has no reported therapeutic effects for the treatment of depressed adolescents (Weersing, Jeffreys et al. 2017). Recently however an attachment-based family therapy model (ABFT) has been tested and does show potential therapeutic effects (Diamond, Russon et al. 2016). ABFT capitalises on the innate, biological desire for meaningful and secure relationships and prioritises relational processes as a treatment focus. The therapy provides an interpersonal, process-oriented and trauma-focused approach to treating adolescent depression, suicidality, and trauma. Further trials are needed to determine if this approach is as or more effective than other evidence based therapies.

Side effects of psychological treatments

Side effects of psychological therapies are less well investigated than those for SSRI medications (see below). When measuring side effects in TADS (such as increase in irritability, agitation and hazardous behaviours) associated with medication these were attenuated when both CBT and an SSRI are delivered concurrently (March, Silva et al. 2004). There was no such attenuation however for combination therapy in the TORDIA study for depressed patients who were pharmacotherapy resistant nor indeed between treatment arms for the IMPACT and the ADAPT studies. Currently we lack data on putative unique side effects accruing directly from psychological therapies (Linden 2013, Jonsson, Alaie et al. 2014).

Antidepressants and therapeutic effects

Considering good methodological trials of depressed adolescents with a rigorous level of measures and monitoring gives efficacy rates some 20-25% greater than placebo (Walkup 2017). The strongest current evidence for efficacy is for fluoxetine. Sertraline and escitalopram have also been shown to be more effective than placebo whereas other SSRIs, mirtazapine and venlafaxine have not been found to be different from placebo. (Cipriani, Zhou et al. 2016, Hetrick, Cox et al. 2016). The TADS study showed that fluoxetine gave a standardised mean difference = 0.51, a moderate to good effect indicating that 69% off those patients were below the mean depression score of the control group. Future pharmacotherapy trials should consider recruiting more severe depressed cases to reduce the incidence of active placebo response more associated with milder disorders as this will provide a more

adequate test of efficacy or effectiveness of medication alone (Bridge, Birmaher et al. 2009).

Side effects of fluoxetine and other antidepressants

Suicidal thoughts are more common in depressed adolescents prescribed an SSRI than those prescribed placebo (Bridge, Iyengar et al. 2007). The pattern of suicide attempts before and after starting medication are however equivalent in those starting fluoxetine with the highest prevalence being just before starting medication and declining thereafter (Simon and Savarino 2007). The rare emergence of disinhibition and switching to mania from depressed mood may be higher amongst depressed adolescents than adults treated with fluoxetine (Baldessarini, Faedda et al. 2013). These switches may occur up to 24 months following the onset of treatment with 3% of depressed patients receiving a diagnosis of bipolar disorder and a further 5% reporting mania like symptoms within 5 years of their unipolar depression. There is no clear evidence that the 'switch' is brought about by antidepressants; it may reflect the natural emergence of mania in an already at-risk population. Manic symptoms at presentation in depressed adolescents are however associated with a poor response to treatment (Maalouf, Porta et al. 2012).

Cost-effectiveness of treating depressed adolescents

Cost-effectiveness analysis is expressed as a ratio between gain in health (measured in improved symptoms or quality of life) and the direct (cost of therapy/treatment and hospital visits) and indirect (time off work, other additional clinic or hospital visits) costs associated with treatment. Treatments with lower cost but known clinical effectiveness may gain greater traction or 'willingness to pay' from service funders. Alternatively, 'willingness to pay' may be acceptable if the cost to the taxpayer or service provider generated by such patients is diminished as a consequence (pay now save later). The IMPACT study reported treatment cost of approximately £1500 per patient (Goodyer, Reynolds et al. 2017). The ADAPT study noted that adding CBT to fluoxetine + specialist clinical care was not cost-effective (Byford, Barrett et al. 2007). The TADS study reported that fluoxetine was more cost-effective than combination therapy or CBT after 12 weeks of treatment (Domino, Burns et al. 2008). By 36 weeks however cost-effectiveness acceptability curves indicated that combination treatment was highly likely (>90%) to be more cost-effective than fluoxetine or CBT alone (Domino, Foster et al. 2009). The TORDIA study showed that combined treatment decreases the number of days with depression but is costlier (Lynch, Dickerson et al. 2011). Here willingness to

pay should be positively influenced by the treatment gains and the possibility of cost reductions in the future.

Therapeutic and clinical course

Treatment response

Improvements in first-episode or treatment-naïve depressed adolescents are often relatively rapid, with around a 25%-30% reduction in symptoms and improved psychosocial functioning over the first 12 weeks. Around 50%-60% of patients with a failed SSRI treatment show good response to combination treatment in the first six weeks (Emslie, Mayes et al. 2010). On average clinical remission (no diagnosis and/or a persistent 50% reduction in baseline symptoms) is maintained in some 80% of trial patients up to a year after end of treatment (Kennard, Silva et al. 2009, Goodyer, Reynolds et al. 2017). Overall clinical progress monitoring should be continued beyond diagnostic change per se until there is a least a 50% drop in symptoms and improvements in function perhaps for at least another 6 months post treatment.

Booster psychological treatment sessions may be advisable in those with increasing symptom during follow up and a 'manage your lifestyle programme' may be advised. For those patients who have responded clinically to fluoxetine, medication reduction should be undertaken with caution and probably not started until there has been at least 6 months stable remission (no longer meeting diagnostic criteria and/or <50% of baseline pre-treatment symptoms).

Treatment non-response

Non-response may occur in up to 40% of depressed adolescents. Thus, non-responsive cases should subsequently receive combination treatment (eg CBT+SSRI). Such a combination may reduce relapse in adolescents who received fluoxetine alone as a first line treatment (Emslie, Kennard et al 2015). Overall treatment response to combination therapies maybe associated with a greater risk reduction for subsequent relapse but this has yet to be fully established using a large enough trial of patients currently in remission (Curry, Silva et al. 2011, Clarke, Mayo-Wilson et al. 2015).

Furthermore around 35% or so of depressed teenagers may drop out of a priori planned treatments, without agreement with the therapist thereby serving an early warning for putative non-response (Warnick, Gonzalez et al. 2012). The IMPACT study reported that poor therapeutic alliance and missed sessions early (eg first month) may index later drop out (O'Keeffe, Martin et al. 2017).

Risk of recurrence or relapse

The likelihood of recurrence and relapse is 50%-75% for successfully treated patients (Kennard, Silva et al. 2009, Vitiello, Emslie et al. 2011). Recurrence can begin within a year implicating the need for greater attention to post-recovery rehabilitation programmes than given hitherto.

Predictors, Moderators, Mediators And Mechanisms Of Treatment Response*Predictors*

There are no demographic factors that reliably predict differences in outcome. In contrast, clinical severity at baseline may be associated with poor treatment response. These include higher levels of depression symptoms, poor global functioning, high levels of suicidality, comorbid anxiety, cognitive distortions, hopelessness, and family conflict (Weersing, Jeffreys et al. 2017).

Moderators

A variable is established as a moderator of treatment response by testing for statistical interactions with two or more treatment options (Brookes, Whitely et al. 2004). In TADS, combined fluoxetine+CBT improved the outcome for mild-moderate depressions but not more severely ill patients (Curry, Rohde et al. 2006). Also from the TADS study, adolescents from high income families responded as well to CBT alone as to combined treatment. In TORDIA, the addition of CBT was more effective in adolescents with more co-morbid disorders (Asarnow, Emslie et al. 2009). Further, in TADS greater self-reported cognitive distortions (catastrophizing, overgeneralization, personalization, and selective abstraction) positively moderated in favour of combined treatment over fluoxetine alone but did not moderate the difference between CBT alone and placebo (Curry, Rohde et al. 2006). There was a marginal positive moderator effect in TORDIA for hopelessness in favour of combined (SSRI+CBT) treatment over monotherapy alone (Asarnow, Emslie et al. 2009). Finally a history of child maltreatment moderates a poorer response to psychological treatments in studies of both treatment naïve and treatment resistant patients (Nanni, Uher et al. 2012).

Mediation and mechanisms

Mediation analysis formally tests measures that may index the processes and mechanisms of the effect of interventions. To date only studies involving CBT have undertaken mediation analyses to determine if therapy altered negative cognitive

biases. Depressogenic thoughts, as indexed by measures of dysfunctional attitudes, negative automatic thinking, cognitive ruminations and negative behavioural styles have all shown some promise as potential mediators, (Kaufman, Rohde et al. 2005, Stice, Rohde et al. 2010). Three factors make any conclusions problematic: first the mediation measures have all been self-reported making a marked confound between antecedent processes and current symptoms; second mediation analyses require temporal separation of the measures for cognitive-behavioural change and symptoms which has not yet occurred; third comprehensive measurement with little or no missing data is required. No study has overcome these problems and had sufficient power and sample size to give valid and replicated findings. There are no mediation studies reported specifically for any SSRI. Mediators may also be revealed in measures of patient treatment expectation and experience such as readiness or motivation to change but this has yet to be tested (Lewis, Simons et al. 2009). Overall there are currently no substantive findings that reveal how psychological or pharmacological treatments mediate outcome.

Prevention of Major Depression

Ideally prevention is better than cure but currently there is no clear-cut strategy that reduces incident onset of depression in the population at large (Stallard, Sayal et al. 2012, Werner-Seidler, Perry et al. 2017). What evidence there is supports a targeted approach aimed at high risk adolescent groups rather than a universal approach delivered to all adolescents with non-clinical but elevated symptoms (Garber, Clarke et al. 2009). Interestingly this program was least effective where there was a currently depressed parent during the treatment. Further long-term effects were maintained by occasional booster sessions to the vulnerable offspring (Brent, Brunwasser et al. 2015).

Issues and Prospects

Behavioural phenotypes and clinical response

There is growing evidence that the manifest characteristics of affective disorders and their comorbidities emerge from a common underlying general latent distress-psychopathology trait, a P factor as it were, where higher P scores reflect the increasing liability for a set of particular clinical signs and symptoms and hazardous behaviours (Brodbeck, Goodyer et al. 2014, Stochl, Khandaker et al. 2015). These bifactor approaches also reveal specific factors independent of each other such as restlessness-fatigue and hopelessness-suicidality. Whether a bi-factorial phenotype will provide

more precision in revealing clinical moderator typologies of treatment remains to be determined.

Adaptive designs

An integrated modular design has been suggested as a more effective alternative to delivering a single treatment modality for mentally ill children and adolescents. The method allows a flexible application of treatments with known efficacy for specific disorders (depression, anxiety, conduct disorder) fitted within a collaborative design. Treatment outcomes were better when compared to usual care (Weisz, Choprita et al. 2012). This modular approach can be viewed as a forerunner of adaptive design which are trials designed to identify which patients are most likely to derive benefit from a particular therapy (Drazen, Harrington et al. 2016). Differing somewhat from the aforementioned modular approach treatments run in sequence with patients who fail a first treatment moving forward to a second treatment and then a third if the second fails and so on (figure one).

Figure One Here.

Before the trial a predefined operational level of clinical improvement is set that results in stoppage of treatment (remission). The trial implementation only considers the % of non-responders as those who have not stopped by end of the treatment sequence not just phase 1. The statistics are more complex but the results define what treatments work best for which patients.

Treatment Guidelines For Practitioners

Current evidence supports a collaborative care approach throughout the treatment period. The evidence base for the treatment of mild depressions is rather equivocal: patients with relatively simple and mild depressions should receive a psychosocial treatment and not receive antidepressants. For moderate to severe and/or complex depression, the decision is not straightforward, as psychological therapies and fluoxetine have advantages and disadvantages. A first line therapy can be a psychological treatment but more severe and complex depressed patients with comorbidities, psychotic phenomenon suicidal and self-harming behaviours should be rapidly assessed for fluoxetine and psychosocial treatment in combination. In some cases, young people and their families may, after full explanation of the options, prefer antidepressants over talking therapy. In such cases, antidepressants as monotherapy

are justified by the evidence. A framework for clinical assessment, treatment and monitoring for depressed adolescents is shown in Figure 2.

Figure two here

Limitations

This is a selected narrative review and the potential effects of studies not included here cannot be gauged. Many studies that tested the efficacy of antidepressants excluded adolescents with suicidality and most co-morbid disorders, making it especially hard to generalise study results to severe and complex cases. The dominance of CBT principled programmes (>85%), makes comparisons between different psychological treatments problematic especially in community and schools based programmes.

Key Practitioner Message

- Major depression episodes are highly treatable and active therapies are more effective than active placebos alone.
- Brief psychosocial therapies, regardless of theoretical orientation, are associated with clinical improvement within 12 weeks in some 70% of cases.
- For complex depression fluoxetine is more effective than placebo, and may be more acutely effective than CBT. There is a greater risk of side-effects (in particular suicidality) which make fluoxetine alone less appropriate than combination therapy as a first-line.
- Lack of response to first-line treatments should lead to combination pharmacological and psychological treatment being offered.

Areas for future research

- Reformulating the clinical phenotype to improve the clinical decision making.
- Urgent investigation of moderator and mediator mechanisms.
- Treatment resistance is in need of considerable further clinical research.
- Clearer evidence required for preventative interventions.
- Evaluating side effects and adverse effects of psychological treatments is long overdue.

Acknowledgements

The IMPACT study was funded by an award to Ian M Goodyer from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 06/05/01). IMG is also supported by a strategic award from the Wellcome Trust to the University of Cambridge and University College London (095844/Z/11/Z).

Table One Randomised Clinical Trials						
Authors	Trial Type	Setting and Target Population	Sample Characteristics	Treatment	Main outcome measures	Outcome
i) Randomised Controlled Trials						
March, Silva, et al.(2004)	RCT	Volunteer sample. 13 US academic and community clinics	12-17 yrs N= 439 MDD	12 wks duration 4 treatment groups 1.Fluoxetine alone (10 to 40 mg/d). 2. CBT alone. 3. CBT with fluoxetine (10 to 40 mg/d) 4.placebo (equivalent to 10 to 40 mg/d).	1. Reduction in CCDRS-R total score. 2. CGI improvement score of 2 or less.	CBT+ fluoxetine and fluoxetine alone both superior to placebo and CBT alone. For CBT+ fluoxetine over control: es = 0.86 NNT = 3
Goodyer, Dubicka et al. et al (2007)	RCT	Clinic-recruited sample 6 NHS CAMHS	11-17yrs n=208 Major or probable major depression.	2 arm design 12 weeks duration. 1.SSRI + care 2.SSRI+ care+ CBT.	1.Reduction in HoNOSCA total score. 2.Reduction in self reported depressive symptoms.	No added value for additional CBT in patients already receiving psychosocial care + fluoxetine
Brent, Emslie et al (2008)	RCT	6 US academic and community clinics. Treatment resistant sample.	n=334 patients 12 to 18 years Primary diagnosis of MDD with no response to 8 wks SSRI.	Twelve wks switch to: 1. A different SSRI (paroxetine, citalopram, or fluoxetine, 20-40 mg). 2. A different SSRI+CBT. 3. Venlafaxine (150-225 mg). 4. Venlafaxine + CBT.	1. CGI improvement. 2. Decrease of > 50% in the CDRS-R.	CBT+ another SRRI resulted in a higher rate of clinical response. es = 0.39 NNT = 7
Stallard, Sayal et al. (2012)	Cluster RCT	Eight UK secondary schools.	N= 1064 Age 12-16 years. high self reported depression symptoms.	3 treatments 1.Group CBT 2.Group attention control. 3.usual school care	Self-reported symptoms of depression at 12 months.	Outcomes were similar for attention control, usual school provision, and cognitive behavioural therapy.

Goodyer, Reynolds et al (2017)	RCT	15 NHS CAMHS sites	N=465 patients Age 11-17 years MDD	3 treatment arms 1.CBT 2.STPP 3.BPI	Self reported depressive symptoms one year after the end of treatment.	No overall superiority between the treatments.
Garber, Clark et al (2009)	RCT	4 USA cities	N= 316 Age 13-17 years 1.Offspring of parents with current or prior depressive illness. 2. Adolescents had a past history of depression, current elevated depressive symptoms.	2 treatment arms: 1.CBTprevent program 2. Usual care alone.	Probable or definite depressive episode.	Depressive episodes were lower for CB prevent. es = 0.2 NNT = 9
Richardson, Ludman et al. (2014)	RCT	Nine primary care clinics	N= 101 Age 13-17 years Screen positive for depression on 2 occasions or MDD	2 arms: 1. Collaborative care 2. Usual care	Change in depressive symptoms on CDRS-R; at 12 months.	Intervention youth had greater decreases in CDRS-R scores. es = 0.71 NNT = 4
Weersing, Brent et al. (2017)	RCT	9 paediatric clinics in 2 cities in the USA	N=185 Age 8.0-17 years Full or probable diagnoses of anxiety and/or depressive disorders	2 treatment arms: 1.Brief behavioural therapy (BBT). 2. Assisted referral to care.	1. CGI improvement score of 2 or less.	clinical improvement greater in BBT group (56.8% vs 28.2%) es = 0.58 NNT = 4,

Table Two: Reviews and Metanalyses						
Authors	Study Type	Target Population	Study Characteristics	Investigation Purpose	Main outcome measures	Outcome
Hetrick, Cox, Merry 2015	Meta-analysis RCTs	N=18,253 43 studies Age 5-19 years	Published or unpublished individual and cluster RCTs.	Efficacy of prevention programmes	Reduction in depression diagnosis	CBT has some effectiveness. Best with targeted populations. Fewer IPT studies but approach appears promising. Too few studies of other interventions.
Cipriani, et al. 2016	Network meta-analysis	34 trials eligible. N= 5260 Age 6-18 years	14 antidepressant treatments.	Efficacy of antidepressant's	Reduction in depressive symptoms.	Only fluoxetine was more effective than placebo.
Hetrick, Cox et al 2016.	Systematic review	N=13,829 participants Aged 5-19 years	Psychological prevention interventions.	Preventing the onset of depressive disorder.	Reduced depression symptoms	Not enough evidence to support the implementation of depression prevention programmes.
Weersing, Jeffreys et al 2017	Narrative review	N = 2659 N=42 studies Age = 13-24 years (mean <18)	Psychological treatments	Efficacy and effectiveness of psychotherapies for existing depression.	Primary outcome of i) reduction in diagnostic cases ii) reduction in depressive symptoms below clinical cut off.	CBT possibly efficacious. IPT promising. No other psychological treatment is studied well enough.
Weisz, Kuppens et al 2017	Metanalysis	N=447 studies N=30,431 participants Age 6-18 years	Psychological therapies youth internalizing and externalizing disorders.	Efficacy and effectiveness of psychological treatment.	Primary outcome of i)% reduction in diagnostic cases ii) reduction in depressive symptoms below clinical cut off.	Behaviour Therapies and CBT showed similar and robust effects. ES = 0.29 Usual care a potent comparison condition.
Werner-Seidler, Perry et al 2017	Systematic review and Metanalysis	N =31,794 participants 81 studies. Age 6-18 years	Psychological prevention.	Efficacy and effectiveness of in schools settings.	depression symptom reduction	Targeted programmes do better than universal. ES = 0.23

Key MDD: Major depressive Disorder; CDRS-R: Children's depression rating Scale –revised ; CGI: Clinical global interview; NNT: Number needed to treat; RCT: randomized controlled trial; es: effect size (hedges g); CBT: Cognitive behaviour therapy; STT: Short term Psychoanalytic Therapy; BPI: Brief Psychosocial Intervention; CBP: Cognitive Behaviour Programme; IPT: Interpersonal Therapy

Figure1:
An Adaptive Design Illustration with Predictor/moderator candidates

- Recruit adolescent depressed patients by diagnosis + self report depression scores.
- Sources can be clinical/community/volunteers.
- Assess potential predictors/moderators of treatment response prior to trial to include:
 - History of child maltreatment/adversities, current comorbidities, self report anxiety , obsessive and antisocial symptoms.
 - Assess current parental depression;
 - Consider adding potential new moderator measures : eg 48 cortisol, polygenic risk profiles, structural imaging networks
- Begin trial with phase 1 below

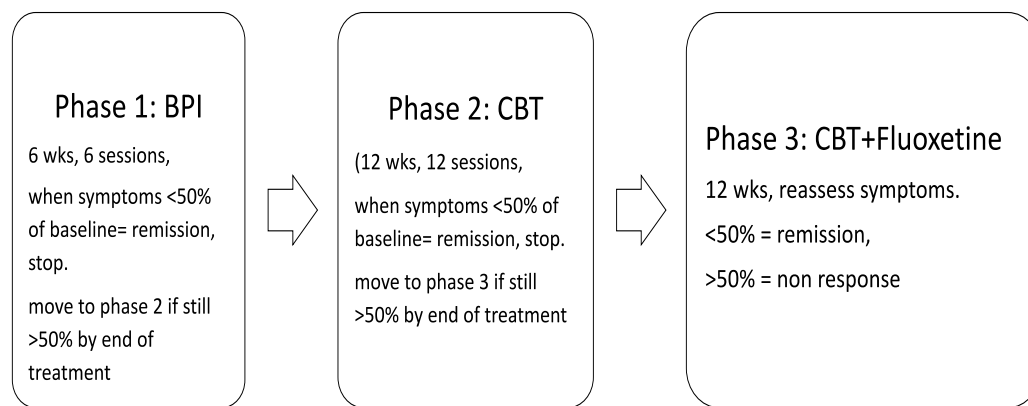
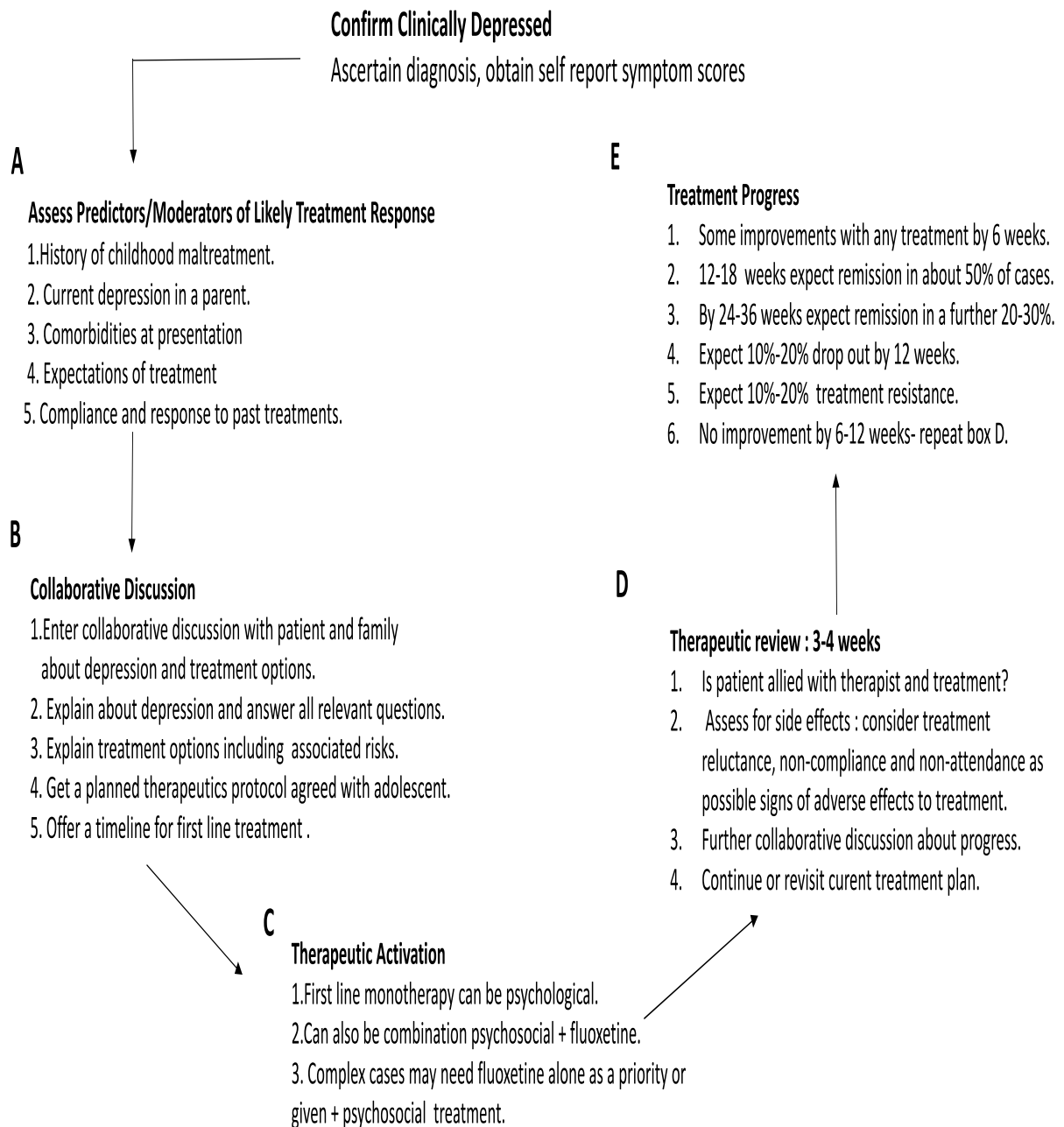


Figure 2 Clinical Assessment, Treatment and Monitoring Framework



References

Asarnow, J. R., G. Emslie, G. Clarke, K. D. Wagner, A. Spirito, B. Vitiello, S. Iyengar, W. Shamseddeen, L. Ritz, J. McCracken, M. Strober, R. Suddath, H. Leonard, G. Porta, M. Keller and D. Brent (2009). Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry*, 48, 330-339.

Baldessarini, R. J., G. L. Faedda, E. Offidani, G. H. Vázquez, C. Marangoni, G. Serra and L. Tondo (2013). Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. *Journal of Affective Disorders*, 15, 129-135.

Brent, D., G. Emslie, G. Clarke, K. D. Wagner, J. R. Asarnow, M. Keller, B. Vitiello, L. Ritz, S. Iyengar, K. Abebe, B. Birmaher, N. Ryan, B. Kennard, C. Hughes, L. DeBar, J. McCracken, M. Strober, R. Suddath, A. Spirito, H. Leonard, N. Melhem, G. Porta, M. Onorato and J. Zelazny (2008). Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*, 299, 901-913.

Brent, D. A., S. M. Brunwasser, S. D. Hollon, V. R. Weersing, G. N. Clarke, J. F. Dickerson, W. R. Beardslee, T. R. Gladstone, G. Porta, F. L. Lynch, S. Iyengar and J. Garber (2015). Effect of a Cognitive-Behavioral Prevention Program on Depression 6 Years After Implementation Among At-Risk Adolescents: A Randomized Clinical Trial. *JAMA Psychiatry*, 72, 1110-1118.

Bridge, J. A., S. Iyengar, C. B. Salary, R. P. Barbe, B. Birmaher, H. A. Pincus, L. Ren and D. A. Brent (2007). Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*, 297, 1683-1696.

Bridge, J. A., B. Birmaher, S. Iyengar, R. P. Barbe and D. A. Brent (2009). "Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder." *American Journal of Psychiatry* 166, 42-49.

Brodbeck, J., I. M. Goodyer, R. A. Abbott, V. J. Dunn, M. C. St Clair, M. Owens, P. B. Jones and T. J. Croudace (2014). General distress, hopelessness-suicidal ideation and worrying in adolescence: concurrent and predictive validity of a symptom-level bifactor model for clinical diagnoses. *Journal of Affective Disorders*, 152-154, 299-305.

Brookes, S. T., E. Whitely, M. Egger, G. D. Smith, P. A. Mulheran and T. J. Peters (2004). Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol* 57(3): 229-236.

Byford, S., B. Barrett, C. Roberts, P. Wilkinson, B. Dubicka, R. G. Kelvin, L. White, C. Ford, S. Breen and I. Goodyer (2007). Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. *British Journal of Psychiatry*, 191,521-527.

Cipriani, A., X. Zhou, ., C. Del Giovane, S. Hetrick, B. Qin, C. Whittington, D. Coghill, Y. Zhang, P. Hazell, S. Leucht, ., P. Cuijpers, J. Pu, D. Cohen., ., A. Ravindran, ., Y. Liu, K. Michael, L. Liu, . and P. Xie (2016). "Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet*, 388,881-890.

Clarke, K., E. Mayo-Wilson, J. Kenny and S. Pilling (2015). "Can non-pharmacological interventions prevent relapse in adults who have recovered from depression? A systematic review and meta-analysis of randomised controlled trials. *Clinical Psychology Review*, 39,58-70.

Curry, J., P. Rohde, A. Simons, S. Silva, B. Vitiello, C. Kratochvil, M. Reinecke, N. Feeny, K. Wells, S. Pathak, E. Weller, D. Rosenberg, B. Kennard, M. Robins, G. Ginsburg, J. March and T. Team (2006). Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*, 45, 1427-1439.

Curry, J., S. Silva, P. Rohde, G. Ginsburg, C. Kratochvil, A. Simons, J. Kirchner, D. May, B. Kennard, T. Mayes, N. Feeny, A. M. Albano, S. Lavanier, M. Reinecke, R. Jacobs, E. Becker-Weidman, E. Weller, G. Emslie, J. Walkup, E. Kastelic, B. Burns, K. Wells and J. March (2011). Recovery and recurrence following treatment for adolescent major depression. *Archives of General Psychiatry* 68, 263-269.

Diamond, G., J. Russon and S. Levy (2016). Attachment-Based Family Therapy: A Review of the Empirical Support. *Family Process*, 55,595-610.

Domino, M. E., B. J. Burns, S. G. Silva, C. J. Kratochvil, B. Vitiello, M. A. Reinecke, J. Mario and J. S. March (2008). Cost-effectiveness of treatments for adolescent depression: results from TADS. *American Journal of Psychiatry*, 165, 588-596.

Domino, M. E., E. M. Foster, B. Vitiello, C. J. Kratochvil, B. J. Burns, S. G. Silva, M. A. Reinecke and J. S. March (2009). "Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the TADS randomized trial. *J Am Acad Child Adolesc Psychiatry*, 48, 711-720.

Drazen, J., D. R. Harrington, J. V. McMurray, J. H. Ware and J. Woodcock (2016). Adaptive Designs for Clinical Trials. *New England Journal of Medicine*, 375, 65-74.

Emslie, G. J., B. D. Kennard, T. L. Mayes, P. A. Nakonezny, J. Moore, J. M. Jones, A. A. Foxwell and J. King (2015). "Continued Effectiveness of Relapse Prevention Cognitive-Behavioral Therapy Following Fluoxetine Treatment in Youth With Major Depressive Disorder." *Journal of the American Academy of Child and Adolescent Psychiatry*, 54, 991-998.

Emslie, G. J., T. Mayes, G. Porta, B. Vitiello, G. Clarke, K. D. Wagner, J. R. Asarnow, A. Spirito, B. Birmaher, N. Ryan, B. Kennard, L. DeBar, J. McCracken, M. Strober, M. Onorato, J. Zelazny, M. Keller, S. Iyengar and D. Brent (2010). Treatment of Resistant Depression in Adolescents (TORDIA): week 24 outcomes. *American Journal of Psychiatry* J Psychiatry, 167, 782-791.

Garber, J., G. N. Clarke, V. R. Weersing, W. R. Beardslee, D. A. Brent, T. R. Gladstone, L. L. DeBar, F. L. Lynch, E. D'Angelo, S. D. Hollon, W. Shamseddeen and S. Iyengar (2009). Prevention of depression in at-risk adolescents: a randomized controlled trial. *JAMA* 301, 2215-2224.

Goodyer, I., B. Dubicka, P. Wilkinson, R. Kelvin, C. Roberts, S. Byford, S. Breen, C. Ford, B. Barrett, A. Leech, J. Rothwell, L. White and R. Harrington (2007). Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. *BMJ* 335, 142.

Goodyer, I. M., S. Reynolds, B. Barrett, S. Byford, B. Dubicka, J. Hill, F. Holland, R. Kelvin, N. Midgley, C. Roberts, R. Senior, M. Target, B. Widmer, P. Wilkinson and P. Fonagy (2017). Cognitive behavioural therapy and short-term psychoanalytical psychotherapy versus a brief psychosocial intervention in adolescents with unipolar major depressive disorder (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled superiority trial. *Lancet Psychiatry*, 4, 109-119.

Goodyer, I. M., S. Reynolds, B. Barrett, S. Byford, B. Dubicka, J. Hill, F. Holland, R. Kelvin, N. Midgley, C. Roberts, R. Senior, M. Target, B. Widmer, P. Wilkinson and P. Fonagy (2017). "Cognitive-behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled trial. *Health Technology Assessment*, 21, 1-94.

Hetrick, S. E., G. R. Cox and S. N. Merry (2015). Where to go from here? An exploratory meta-analysis of the most promising approaches to depression prevention programs for children and adolescents. *International Journal of Environmental Research and Public Health*, 12, 4758-4795.

Hetrick, S. E., G. R. Cox, K. G. Witt, J. J. Bir and S. N. Merry (2016). Cognitive behavioural therapy (CBT), third-wave CBT and interpersonal therapy (IPT) based interventions for preventing depression in children and adolescents. *Cochrane Database Syst Rev*, CD003380.

Jonsson, U., I. Alaie, T. Parling and F. K. Arnberg (2014). "Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: a review of current practice. *Contemporary Clinical Trials*, 38,1-8.

Kaptchuk, T. J. and F. G. Miller (2015). Placebo Effects in Medicine. *New England Journal of Medicine* 373, 8-9.

Kaufman, N. K., P. Rohde, J. R. Seeley, G. N. Clarke and E. Stice (2005). Potential mediators of cognitive-behavioral therapy for adolescents with comorbid major depression and conduct disorder. *Journal of Consulting and Clinical Psychology*, 73, 38-46.

Kennard, B. D., S. G. Silva, S. Tonev, P. Rohde, J. L. Hughes, B. Vitiello, C. J. Kratochvil, J. F. Curry, G. J. Emslie, M. Reinecke and J. March (2009). Remission and recovery in the Treatment for Adolescents with Depression Study (TADS): acute and long-term outcomes. *J Am Acad Child Adolesc Psychiatry*, 48,186-195.

Klerman, G. L., S. Budman, D. Berwick, M. M. Weissman, J. Damico-White, A. Demby and M. Feldstein (1987). Efficacy of a brief psychosocial intervention for symptoms of stress and distress among patients in primary care. *Medical Care*, 25,1078-1088.

Kraemer, H. C. and C. Blasey (2015). *How Many Subjects? Statistical Power Analysis in Research*. Los Angeles, Sage Publications.

Lewis, C. C., A. D. Simons, S. G. Silva, P. Rohde, D. M. Small, J. L. Murakami, R. R. High and J. S. March (2009). The role of readiness to change in response to treatment of adolescent depression. *Journal of Consulting and Clinical Psychology* 77(3): 422-428.

Linden, M. (2013). How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. *Clinical Psychology and Psychotherapy*, 20, 286-296.

Lynch, F. L., J. F. Dickerson, G. Clarke, B. Vitiello, G. Porta, K. D. Wagner, G. Emslie, J. R. Asarnow, Jr., M. B. Keller, B. Birmaher, N. D. Ryan, B. Kennard, T. Mayes, L. DeBar, J. T. McCracken, M. Strober, R. L. Suddath, A. Spirito, M. Onorato, J. Zelazny, S. Iyengar and D. Brent (2011). Incremental cost-effectiveness of combined therapy vs medication only for youth with selective serotonin reuptake inhibitor-resistant depression: treatment of SSRI-resistant depression in adolescents trial findings. *Archives of General Psychiatry* 68, 253-262.

Maalouf, F. T., G. Porta, B. Vitiello, G. Emslie, T. Mayes, G. Clarke, K. D. Wagner, J. R. Asarnow, A. Spirito, M. Keller, B. Birmaher, N. Ryan, W. Shamseddeen, S. Iyengar and D. Brent (2012). Do sub-syndromal manic symptoms influence outcome in treatment resistant depression in adolescents? A latent class analysis from the TORDIA study. *Journal of Affective Disorders*, 138, 86-95.

March, J., S. Silva, S. Petrycki, J. Curry, K. Wells, J. Fairbank, B. Burns, M. Domino, S. McNulty, B. Vitiello, J. Severe and T. Treatment for Adolescents With Depression Study (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial, *JAMA*, 292,807-820.

Nanni, V., R. Uher and A. Danese (2012). "Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *American Journal of Psychiatry* 169, 141-151.

O'Keeffe, S., P. Martin, I. M. Goodyer, P. Wilkinson, I. Consortium and N. Midgley (2017). "Predicting dropout in adolescents receiving therapy for depression. *Psychother Research*, 1-14.

Richardson, L. P., E. Ludman, E. McCauley, J. Lindenbaum, C. Larison, C. Zhou, G. Clarke, D. Brent and W. Katon (2014). "Collaborative care for adolescents with depression in primary care: a randomized clinical trial. *JAMA* 312, 809-816.

Simon, G. E. and J. Savarino (2007). Suicide attempts among patients starting depression treatment with medications or psychotherapy. *American Journal of Psychiatry*, 164, 1029-1034.

Stallard, P., K. Sayal, R. Phillips, J. A. Taylor, M. Spears, R. Anderson, R. Araya, G. Lewis, A. Millings and A. A. Montgomery (2012). Classroom based cognitive behavioural therapy in reducing symptoms of depression in high risk adolescents: pragmatic cluster randomised controlled trial. *BMJ*, 345,e6058.

Stice, E., P. Rohde, J. R. Seeley and J. M. Gau (2010). "Testing mediators of intervention effects in randomized controlled trials: An evaluation of three depression prevention programs. *Journal of Consulting and Clinical Psychology*, 78, 273-280.

Stochl, J., G. M. Khandaker, G. Lewis, J. Perez, I. M. Goodyer, S. Zammit, S. Sullivan, T. J. Croudace and P. B. Jones (2015). Mood, anxiety and psychotic phenomena measure a common psychopathological factor. *Psychological Medicine*, 45, 1483-1493.

Vitiello, B., G. Emslie, G. Clarke, K. D. Wagner, J. R. Asarnow, M. B. Keller, B. Birmaher, N. D. Ryan, B. Kennard, T. L. Mayes, L. DeBar, F. Lynch, J. Dickerson, M. Strober, R. Suddath, J. T. McCracken, A. Spirito, M. Onorato, J. Zelazny, G. Porta, S. Iyengar and D. A. Brent (2011). Long-term outcome of adolescent depression initially resistant to selective serotonin reuptake inhibitor treatment: a follow-up study of the TORDIA sample. *Journal of Clinical Psychiatry* 72, 388-396.

Walkup, J. T. (2017). Antidepressant Efficacy for Depression in Children and Adolescents: Industry- and NIMH-Funded Studies. *American Journal of Psychiatry*, 174, 430-437.

Warnick, E. M., A. Gonzalez, R. V. Weersing, L. Scahill and J. Woolston (2012). Defining dropout from youth psychotherapy: how definitions shape the prevalence and predictors of attrition. *Child and Adolescent Mental Health*, 17, 76-83.

Weersing, V. R., M. Jeffreys, M. T. Do, K. T. Schwartz and C. Bolano (2017). Evidence Base Update of Psychosocial Treatments for Child and Adolescent Depression. *Journal of Clinical Child and Adolescent Psychology*, 46, 11-43.

Weisz, J. R., B. F. Chorpita, L. A. Palinkas, S. K. Schoenwald, J. Miranda, S. K. Bearman, E. L. Daleiden, A. M. Ugueto, A. Ho, J. Martin, J. Gray, A. Alleyne, D. A. Langer, M. A. Southam-Gerow, R. D. Gibbons and H. Research Network on Youth Mental (2012). Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth: a randomized effectiveness trial. Archives of General Psychiatry **69**, 274-282.

Weisz, J. R., S. Kuppens, M. Y. Ng, D. Eckshtain, A. M. Ugueto, R. Vaughn-Coaxum, A. Jensen-Doss, K. M. Hawley, L. S. Krumholz Marchette, B. C. Chu, V. R. Weersing and S. R. Fordwood (2017). What five decades of research tells us about the effects of youth psychological therapy: A multilevel meta-analysis and implications for science and practice. *American Psychologist*, *72*, 79-117.

Werner-Seidler, A., Y. Perry, A. L. Calear, J. M. Newby and H. Christensen (2017). School-based depression and anxiety prevention programs for young people: A systematic review and meta-analysis. *Clinical Psychology Reviews* *51*, 30-47.