IN CONTEXT

In Context: Lessons About Adolescent Unipolar Depression From the Improving Mood With Psychoanalytic and Cognitive Therapies Trial

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This review paper summarizes the results of the Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT) study and its implications for psychological treatment of adolescents with moderate to severe unipolar major depression. IMPACT was a pragmatic, superiority, randomized controlled trial conducted in the United Kingdom, which compared the clinical and cost-effectiveness of short-term psychoanalytic therapy (STPP), cognitive–behavioral therapy (CBT), and a brief psychosocial intervention (BPI) in reducing depression symptoms in 465 adolescents with unipolar major depression, aged 11 to 17 years. Although this was a clinically heterogeneous group of adolescents, some symptoms (eg, sleep and concentration difficulties, irritability/anger) were common and disabling. The trial reported no significant difference among the 3 treatments in reducing depression symptoms. One year after treatment, 84% of participants showed improvement in depressive symptoms (<50% of baseline symptoms) and improved psychosocial functioning, achieving this through different symptom reduction trajectories. Although participants attended fewer treatment sessions than planned, the 3 treatments were delivered with fidelity to their respective models. Ending treatment without therapist agreement occurred in 37% of cases. This was not associated with outcomes by treatment group. Adolescents emphasized the importance of the therapeutic relationship in all 3 treatments. Results suggest that although most adolescents respond to time-limited, structured psychological therapy, subgroups of depressed adolescents are likely to need additional treatment or support. These include adolescents who live in complex circumstances and/or who believe that their needs are not met in therapy, some who stop treatment early, and the 16% to 18% of adolescents who do not respond to treatment.

Clinical trial registration information: Improving Mood and Preventing Relapse With Psychoanalytic Psychotherapy and Cognitive Behaviour Therapy; https://www.isrctn.com; ISRCTN83033550.

Key words: depression; adolescent; treatment; randomized controlled trial; psychological therapy

J Am Acad Child Adolesc Psychiatry 2023;■(■):■-■.

Adolescent depression is common[1] and debilitating,[2-5] and is associated with unfavorable outcomes into adulthood.[6-8] Therefore, there is an individual and societal need to provide effective treatments for adolescent depression that are both clinically and economically viable. Despite investment in developing and evaluating psychological treatments for adolescent depression, benefits are modest,[9-11] and there are major gaps in our understanding of what kind of treatment is most effective.

Our aim is to summarize and synthesize the many findings from the Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT) study, the largest clinical trial worldwide of treatment for major depression in adolescence. The trial has resulted in more than 100 peer-reviewed papers, 3 books, and many postgraduate dissertations and theses. Our objectives are as follows: (1) to provide a succinct overview of the IMPACT study, and (2) to offer a narrative synthesis of the published results and to consider their implications for clinical practice.

Background to the IMPACT Study

When the UK National Institute of Health and Clinical Excellence (NICE) published their first guidelines on the treatment of child and adolescent depression in 2005, cognitive–behavioral therapy (CBT) was recommended as the psychotherapy of choice with short-term psychodynamic psychotherapy (STPP) and interpersonal psychotherapy (IPT) suggested as potentially helpful. Given the modest evidence base, the National Institute of Health Research Health Technologies Assessment Committee

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(a UK government–backed funding agency) called for bids to investigate psychological treatment effectiveness for depressed adolescents. The successful bid was the IMPACT study,[12] a pragmatic randomized controlled trial comparing the effectiveness of 2 specialist psychological treatments—CBT and STPP—and a brief psychosocial intervention (BPI), each delivered in routine adolescent mental health National Health Service (NHS) practice in England.

The 3 treatment arms were representative of what an adolescent referred to a child and adolescent mental health service (CAMHS) in the United Kingdom would likely have been offered for treating depression at the time that the study was designed.[13] CBT aims to help adolescents to identify thoughts and behaviors that maintain depression, and to work with their therapist to challenge unhelpful thoughts and to change unhelpful thoughts and behaviors[14,15]. CBT in IMPACT included up to 20 sessions, delivered over 30 weeks by a specialist CAMHS clinician with a core mental health training and post qualification experience in CBT, but not necessarily accredited by the British Association of Behavioural and Cognitive Psychotherapies. The CBT treatment manual focused on engaging the adolescent in therapy and included the option of caregivers attending sessions with the adolescent. STPP aims to help adolescents to develop a better understanding of their emotional experiences, in order to support personal growth and the negotiation of developmental tasks. STPP included up to 28 individual sessions, plus 7 caregiver sessions to be delivered within 30 weeks.[16,17] All STPP therapists were child and adolescent psychotherapists accredited by the Association of Child Psychotherapists. BPI is an information-giving and action-oriented intervention focused on psychoeducation about depression and mental states, prescribing interpersonal activities and enhancing personal performance, and setting goals (https://www.cambridgebpi.com). Unlike CBT and STPP, BPI did not focus on cognitive components of depression or on promoting self-understanding. BPI included up to 12 sessions over 20 weeks, delivered by specialist CAMHS clinicians, primarily child and adolescent psychiatrists and mental health nurses. Four of these could be family sessions.

Design of the IMPACT Study

This multicenter, observer-blind, randomized controlled superiority trial investigated the effectiveness and cost-effectiveness of cognitive–behavioral therapy (CBT), short-term psychoanalytic psychotherapy (STPP), and a brief psychosocial intervention (BPI) on the reduction of depression symptoms in adolescents (N = 465) up to 1 year after the end of treatment. Adolescents aged 11 to 17 years who met the diagnostic criteria for major depressive disorder (MDD) were recruited from 15 routine clinics across 3 geographical regions in England (ie, the cities of London and Manchester and predominantly rural East Anglia). Adolescents were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS),[18] and those who had confirmed MDD were randomized to one of the 3 psychological treatment arms. The baseline characteristics of the participants are shown in Table 1.[19] Adolescents were treated within their routine practice setting and reassessed at a nominal 6-, 12-, 36-, 52-, and 86-week follow-up from randomization.

The primary outcome measure of depression symptoms was the 33 item self-report Mood and Feelings Questionnaire (MFQ)[20] Secondary outcomes included psychosocial functioning,[21] self-reported anxiety,[22] obsessionality,[23] and antisocial behavior difficulties[24] (see Table 2 for summary of main measures used). All adolescents and parents completed the K-SADS at baseline, end of treatment, and end of study. The plan of the study and the flow of adolescents though the study is shown in Figure 1.

Alongside the main trial, 3 substudies took place, which aimed to provide multiple perspectives on adolescent depression and treatment. The participants in the substudies were opportunity-based samples, with additional consent to participant. These studies were embedded in the trial design as secondary studies, recruiting patients from the trial cohort as they became available until their pre-planned sample size was achieved. These were as follows:

1) the IMPACT-My Experience (IMPACT-ME) study,[25] a qualitative study of the experience of depression and treatment that included 81 adolescents consecutively recruited from the North London center. Interviews were conducted with adolescents and separately with their parents at pre-treatment, post-treatment, and 1-year follow-up. In cases in which adolescents gave permission, their therapists were also interviewed post-treatment.
2) the Magnetic Resonance–IMPACT (MR-IMPACT) study,[26] which included 128 adolescents recruited from the East Anglia and North London centers and 40 healthy age-/sex-matched controls who answered invitations to participate that were placed in a school in Cambridge. All participants underwent structural and functional neuroimaging at baseline, with 75 patients (all in the CBT arm of the study) completing a second scan after treatment.
3) an endocrine study,[27] which invited 279 participants from the trial cohort from all 3 centers to collect saliva samples pre-treatment to investigate the moderating effects of morning and evening salivary cortisol levels on treatment response.

TABLE 1 Baseline Characteristics of the Participants in the IMPACT Study

Characteristic	BPI (n = 155)	CBT (n = 154)	STPP (n = 156)
Age, y	15 (11-17)	15 (12-17)	15 (11-17)
Sex			
Male	40 (26%)	40 (26%)	37 (24%)
Female	115 (74%)	114 (74%)	119 (76%)
Ethnic origin			
White[a]	121/147 (82%)	131/152 (86%)	130/151 (86%)
Region			
East Anglia	61 (39%)	62 (40%)	62 (40%)
North London	43 (28%)	41 (27%)	43 (27%)
Northwest	51 (33%)	51 (33%)	51 (33%)
Conduct or oppositional disorder	20 (13%)	20 (13%)	16 (10%)
Self-reported depression score	46·2 (10·6)	46·2 (10·3)	45·4 (10·8)
Number of interviewer-assessed depressive symptoms	8·4 (2·5)	8·7 (2·3)	8·3 (2·5)
SSRI prescribed before trial entry[b]	29/153 (19%)	32/125 (21%)	28/155 (18%)
Prevalence of 1 or more comorbid *DSM-5* axis 1 psychiatric diagnoses	71 (46%)	80 (52%)	74 (47%)
One or more recent suicide attempts[c]	3 (2%)	2 (1%)	7 (5%)
Lifetime suicide attempts	57 (37%)	48 (31%)	55 (35%)
Recent self-harm attempts[c]	26 (17%)	25 (16%)	34 (22%)
One or more lifetime non-suicidal self-injury episodes	87 (56%)	75 (49%)	84 (54%)
HoNOSCA score	18·9 (6·0)	18·4 (6·0)	18·3 (6·3)
EQ-5D score	0·596 (0·27)	0·578 (0·58)	0·569 (0·59)

Note: Adapted from Goodyer et al.[19] *(pp. 109-119), with permission from the publisher. Data are median (range), n (%), or mean (SD). BPI = brief psychological intervention; CBT = cognitive–behavioral therapy; EQ-5D = EuroQol 5 dimensions questionnaire; HoNOSCA = Health of the Nation Outcome Scales for Children and Adolescents; IMPACT = Improving Mood With Psychoanalytic and Cognitive Therapies; SSRI = selective serotonin reuptake inhibitors; STPP = short-term psychoanalytical psychotherapy.*

[a]*Detailed information on ethnicity was not collected in the original IMPACT study. This figure excludes 15 patients for whom ethnic group or origin was not stated or was missing.*

[b]*Excludes 5 patients with missing information.*

[c]*In the previous 2 weeks.*

WHAT DID WE LEARN ABOUT THE CHARACTERISTICS OF DEPRESSION IN ADOLESCENTS?

Presenting Clinical Characteristics

A total of 557 clinic-referred adolescents were identified and assessed; 87 (16%) did not meet criteria and 470 were randomly assigned, with 465 entering the study. The median age of the participants was 15.6 years and 75% were female. Data on ethnicity was poorly collected and so cannot be reported on in any detail. At baseline, the recruited participants had a mean MFQ score of 45.9 (SD = 10.5); most (>90%) were experiencing their first episode of MDD, and the majority were clinically assessed as moderately to severely depressed with marked personal and social impairments. Full details of case identification, assessment, and recruitment are described in the IMPACT Monograph (chapter 9)[24] and in the main outcomes paper.[19]

The most common symptom reported by participants was insomnia/hypersomnia (92% of participants), and over 70% reported problems with concentration, lack of energy, and low mood and/or irritability. More than half of the participants reported experiencing 1 or more of the depression symptoms worthlessness, anhedonia, irritability, or suicidal ideation, with fewer than 20% reporting changes in weight or appetite. Delusions or hallucinations (around 10%) and current suicidal acts (3%) were rare, but 34% reported at least 1 past suicide attempt. Adolescents' experiences of depression at baseline were explored through semi-structured interviews (n = 77).[28] Depressed mood, loss of interest or pleasure, change in sleep patterns, low energy, low self-esteem, poor concentration, and thoughts of suicide or death were prominent in these narrative accounts, resonating with the K-SADS diagnostic assessments. Interestingly, many of the depressed adolescents spoke about difficulties with

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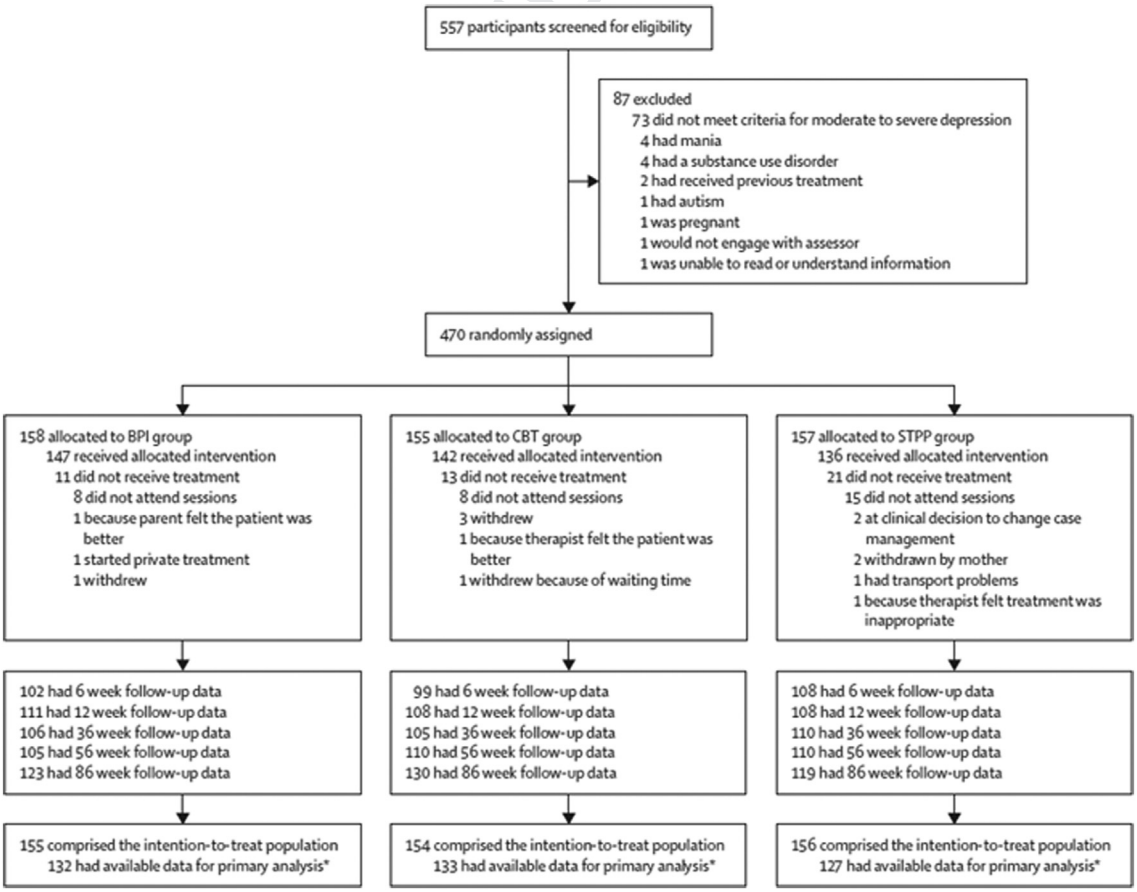
TABLE 2 Summary of Main Measures Used in the IMPACT Study

IMPACT Self-Report Questionnaires	Item No.	Purpose of the Scale[a]
Mood and Feelings (MFQ)	33	Sum score measures the overall frequency of depression symptoms present in the last 2 weeks
Revised Manifest Anxiety Scale (RMAS)	28	Sum score assesses the current level and nature of anxiety
Short Form Leyton Obsessional Inventory (LOI)	11	Sum score measures the current level and nature of obsessional thoughts and compulsive behaviors
Antisocial Behavior (ASB)	11	Sum score measures the level and nature of current antisocial behaviors
Health of the Nation Scale (HoNOSCA)	13	Measures the severity and nature of problems and psychosocial impairments

Note: *IMPACT = Improving Mood With Psychoanalytic and Cognitive Therapies.*
[a]*All items were rated on a 4-point scale (never, sometimes, mostly, or almost always). Responses of "mostly" and "almost always" were collapsed.*

anger. Although irritability was often recorded in the K-SADS interviews, more extreme feelings of anger were commonly identified in the narrative accounts. A further comparison of features of depression described by the participants compared to a range of depression measures suggests that widely used measures of adolescent depression may not fully capture key elements of adolescents' experiences.[29]

FIGURE 1 Flow Chart of Adolescents Through the Study CONSORT Diagram



Note: *Adapted from Goodyer* et al.[19] *(pp. 109-119), with permission from the publisher.*

Before treatment, most adolescents wished to understand why they had become depressed, and althogh some emphasized biological/genetic explanations, many understood their depression as a response to psychosocial stressors. They also wanted to help other adolescents to understand and recognize when they were depressed, and the importance of seeking help. This led to co-creation with a group of adolescents[30] of a short film, "Facing Shadows," which has been used as psychoeducation in schools and colleges (https://www.youtube.com/watch?v=LdmRPKUhNEY).

Parents' Experiences of Their Children's Depression

A thematic analysis of semi-structured pre-treatment interviews with 48 parents of participants revealed parents' "lack of awareness" about their adolescent experiencing depression or any problem at all. Parents also reported "emotional turmoil" and feelings of "helplessness" in themselves, together with "parenting in overdrive" behaviors.[31] These findings suggest that psychoeducation or other forms of therapeutic support for parents of depressed adolescents may also be valuable to help them to navigate and concurrently support their child's treatment and recovery. A group of parent participants co-created a short film about the experience of parenting an adolescent child with depression (https://www.youtube.com/watch?v=IuU81p-lVe4).

WHAT DID WE LEARN ABOUT TREATMENT EFFECTIVENESS?

Clinical Symptoms and Diagnoses

One year post-treatment, there were no significant differences between treatments on self-reported depression severity; each had reduced depression symptoms by 49% to 52% from baseline.[24] The results were the same for secondary outcomes of self-reported anxiety, obsessive-compulsive symptoms, and antisocial/oppositional behaviors, and for interviewer-assessed diagnoses and personal and social impairment. Both age and sex were covariates in all primary analyses and were non-significant in all results.

By the end of treatment (36 weeks after randomization) and end of the study (86 weeks after randomization), reductions in self-reported depression symptoms were respectively 39% and 53% from baseline. Adolescents reported comparable reductions in their anxiety, anti-social behavior, and obsessive-compulsive symptoms from baseline to the end of treatment and end of the study. Adolescent psychosocial functioning, using the interviewer-rated HoNOSCA,[21] were respectively 43% and 58% after treatment and end of the study. Adaptive functioning assessed using the HoNOSCA indicated an average 8-point improvement at the end of treatment and 10-point improvement by the end of the study. The percentage of adolescents who no longer met diagnostic criteria for a major depressive episode by the end of treatment and end of the study were 63% and 77%, respectively. However, although these binary clinical data are an index of possible diagnostic change, we suggest that they be interpreted with caution. The study was not powered on a binary outcome, and the burden of full clinical interviews using the K-SADS diagnostic interview was too great for many adolescents and families over the duration of trial, meaning that only 61% of participants and their parents completed the clinical interviews post-treatment. Adolescent self-report of depressive symptom severity on the Mood and Feelings Questionnaire (MFQ) suggested that over 80% experienced clinically and statistically significant improvement. In contrast, full clinical remission (ie, no diagnosis of depression and above threshold for psychosocial function) appeared to be less common, with about two-thirds of case participants entering remission by the end of the study.

Treatment Dose and Duration

These equivalent clinical outcomes across the 3 treatments were achieved across the same amount of time but with different treatment "doses" (ie, the number [n] of sessions). Although the differences were not statistically significant, BPI required fewer sessions (median = 6 sessions, IQR = 4, 11; mean duration = 27.5 weeks, SD = 21.5) than CBT (median = 9 sessions, IQR = 5, 14; mean duration = 24.9, SD = 17.7) or STPP (median = 11 sessions, IQR = 5, 23; mean duration = 27.9, SD = 16.8). Interestingly, on average, no treatment delivered more than 50% of the preplanned treatment sessions (ie, 12 for BPI, 20 for CBT, 28 + 7 parent sessions for STPP) as intended per protocol. There was no effect of the number of treatment sessions attended on the primary or secondary outcomes.

Cost-Effectiveness

Health economic analysis included the direct costs of treatment, and the subsequent use of health and care services. The total cost of interventions over the study did not differ among the treatment arms, which probably reflected the salary differentials of the staff delivering different treatments; BPI was delivered in around 70% of cases by medical psychiatry and 30% by senior mental health nurses; CBT by psychologists, mental health nurses, and occupational therapists; and STPP by child and adolescent psychotherapists.

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Adverse Effects

Adverse physical effects were not significantly different between treatments. We noted that adverse and side effects measures are designed primarily for medication trials, and reliable and valid measurement of psychotherapy side effects was not available. We examined the dropout rate from treatment as a proxy measure of a potential treatment side effects, and found no statistically significant dropout rate differences between treatment groups.[32]

CLINICAL PHENOTYPES AND TREATMENT RESPONSE

Symptoms, Clusters, and Factors

Sleep difficulties (insomnia/hypersomnia), which were the most prevalent symptoms at baseline, decreased significantly irrespective of treatment arm, although, interestingly, half of the adolescents who experienced sleep difficulties continued to report these by the end of the study.[33] Adolescents themselves conceptualized sleep difficulties as being due to ruminative thinking, such as intrusive feelings of helplessness.[34] Psychological treatment that includes a focus on improving adolescents' perceived loss of ability to evoke sleep may help to reduce residual sleep difficulties as well as contribute to reducing depression symptoms overall.[33]

Although not a predictor of treatment response *per se,* a latent class analysis[35] of K-SADS depression symptoms at baseline identified a significant cluster (21%) of participants who can be described as having lower levels of symptoms (mean symptom level of 6 compared to 9 for the total sample), characterized by predominantly somatic symptoms accompanied by very low levels of negative cognitions. In this class of participants, 100% experienced insomnia/hypersomnia symptoms, and over 90% reported problems with concentration, slow thinking, or indecisiveness. In addition, less than 10% reported suicidality over their lifetime whereas 33% described current feelings of worthlessness (compared with 59% and 78% of the total sample, respectively); there were as many male participants as female participants in this subgroup (total sample, 75% female participants). This "somatic" class of participants experienced less severe symptoms at baseline but was as likely to respond to treatment. In contrast, they showed somewhat less continued recovery in the follow-up period than the sample as a whole.[35] Sleep difficulties in this group may be associated with intrusive thoughts, based on the qualitative findings[34] described above. We suggest that practitioners and primary care services need to be aware that as many as 1 in 5 depressed adolescents may have an atypical constellation of symptoms at presentation characterized by physical or somatic difficulties. Unlike insomnia/hypersomnia, psychotic symptoms in theory may index more severe depression and a worse prognosis. In this sample of depressed adolescents, psychotic symptoms were uncommon, and they did not predict treatment response or sensitivity to treatment type.[36]

The self-reported measures of depression, anxiety, obsessionality, and antisocial behavior, together with that of psychosocial function, were assessed at all 6 time points of the study. Longitudinal methods were used to examine whether the additional information obtained over time improved the sensitivity of the associations among the behavioral phenotype, treatment response, and outcome. Longitudinal growth mixture modeling was used on the primary outcome self-report measure of depression.[37] The participants were categorized into 2 classes, with initially similar and subsequently markedly distinct trajectories. In both groups, depression symptoms declined significantly over the first 18 weeks. Of the participants, 84% (n = 391), that is, the "continued-improvers," reported symptoms that reduced further over the duration of the study. A total of 16% were termed "halted-improvers"; these participants had higher depression scores at baseline, were more likely to have an additional mental health diagnosis, and reported faster recovery in the first 18 weeks but no further improvement. Overall, most depressed adolescents continued to improve in the 12 months following the end of the psychological therapy, and for some it was 12 to 18 weeks before they responded to treatment. This suggests that clinicians should be wary of self-reported rapid improvement in the first 6 to 12 weeks in patients with severe depression. Such individuals are at risk for early relapse.

Given the improvements, a second investigation sought to build on the above to determine whether studying the broader phenotype would improve precision between treatment type and clinical response, using all of the self-report sum scores in a longitudinal bi-factor model.[38] This analysis identified a longitudinal 'general psychopathology' (p) factor which decreased in all participants regardless of therapy type by the end of study. Five specific factors were also identified, with differing trajectories of change. There were protracted improvements in general psychopathology and conduct problems. However, the specific factor "melancholic and negative cognitions" decreased only to 6 weeks and then remained unchanged. The obsessive-compulsive factor did not change throughout. The anxiety factor increased in the first 6 weeks and then reverted to baseline levels throughout. Continuing improvements in general psychopathology and conduct problems subsequently occured. Following this analysis, a

growth mixture latent class approach[39] using the same factors showed that as well as overall clinical equivalence, there was no difference in the rate and pace of change among treatments over time.

Combining Fluoxetine With Psychological Therapy

The IMPACT trial was a comparison of 3 psychological therapies, delivered within routine mental health services and following national guidance where relevant. The trial protocol indicated that fluoxetine could be prescribed to any participant in any arm if they met NICE criteria[13] for doing so: that is, not responding to or showing signs of deterioration while receiving psychological treatment. Because fluoxetine was not a protocol-driven treatment, comments on its prescribing during the trial are observational only. A similar proportion of participants in each treatment arm (27%) were prescribed medication during the trial treatment period. IMPACT was not designed to evaluate the effects of fluoxetine or of combination therapy; however, including selective serotonin reuptake inhibitors (SSRIs) in the longitudinal data analyses had no effects on any of the results outlined above.[40] No other psychotropic medications were medications prescribed during the trial.

The qualitative analysis of adolescents' experiences of being recommended an SSRI revealed that within this age range, medication may not be seen as a desirable introduction, even if considered clinically necessary. Among the themes identified, were that antidepressants: (1) validated the severity of their illness, (2) were a support, not a solution, (3) were a tool to aid recovery rather than a treatment itself, and (4) entailed an ongoing process of trial and error.[41] These subjective reports note the clear importance of practitioners needing to be collaborative and clear in their communications with the adolescent when fluoxetine is being considered as a treatment.

Markers of Treatment Response

The imaging sub-study, IMPACT-MR, aimed to identify neural changes associated with psychological treatment response.[26] Pre-treatment imaging measures compared case participants with controls on the following: (1) structural measures of gray and white matter volume and cortical thickness, (2) resting-state functional connectivity (rsFC), and (3) responses to an affective Go/No-Go task.

Cross-Sectional Findings

The cross-sectional findings on brain structure showed that, compared to controls, depressed patients had greater cortical thickness within the subgenual anterior cingulate and medial orbitofrontal cortex. Patients also showed greater white matter volume within the frontal regions of the brain: specifically, in the bilateral medial frontal gyri, bilateral superior frontal gyri, and right middle frontal gyrus.[36] In contrast, there were no group differences in gray matter volume.[42] None of these cross-sectional structural findings were corelated with self-reported depression or anxiety symptoms at baseline.[36]

From a functional perspective, increases in rsFC were found in patients compared to controls in the right superior frontal gyrus, right subgenual anterior cingulate, and right amygdala. There was no association between white matter thickness and volume and rsFC.[36] Again, there were no significant correlations between mean regional rsFC differences and baseline symptoms of depression and anxiety.

Longitudinal Findings

There were no changes over time in any of the structural measures. This suggests that there is no clear-cut treatment response marker in white matter volume or structure. Overall greater cortical thickness and volume may not be a consequence of depression illness effects. There may be more long-standing differences in brain maturation indexed between depressed and non-depressed adolescent brains, perhaps because of prior disruptions in the environment, previous mental illnesses, or genetic variation influencing neural development. For example, increased expression of psychopathology during adolescence appears to be closely linked to lower rates of myelin maturation in selective brain tracts over time.[43] The functional consequences of myelin impairment during adolescence may include retaining a larger-than-expected degree of preference uncertainty, expected in childhood, resulting in an over-reliance on the influence of others during adolescence on making decisions.[44]

Both increases and decreases in rsFC were noted between baseline and post-treatment. These were modest in size and were found in a range of brain regions. Interestingly, changes in rsFC were weakest within regions that showed the greatest pre-treatment functional disruption (ie, right superior frontal gyrus, right subgenual anterior cingulate, and right amygdala). Consequently, the more densely connected neurons in these regions observed pre-treatment did not show normalizing effects following treatment. Therefore, pre-treatment functional disruption did not overlap with the regions showing post-treatment changes in rsFC.[36] Finally, there were no correlations between changes in rsFC and changes in self-rereported depressive or anxious sum scores.

Regions showing the greatest functional disruption pre-treatment may be slower to respond and may need more time to recover. Furthermore, increases in rsFC in regions not identified pre-treatment may indicate a growing neural functional disruption, namely, treatment non-response or a treatment-sensitive enhancement of areas under-functioning in the pre-treatment illness phase, or a modest decline in overly dense connections in some regions.[44,45] These alternatives suggest that future studies should include longitudinal rsFC scans at 12 and 18 months post-treatment, to help determine the therapeutic and prognostic importance of differential rsFC change during and after psychotherapy. Finally, the affective Go/No-Go task showed aberrant brain hyperactivity to positive distractors, which normalized in some participants after CBT and may deserve further evaluation as a treatment response marker.[45] However, reliable implementation of such a task in routine clinical practice may be difficult.

Overall, the IMPACT-MR study reveals neural structure and functional connectivity characteristics in depressed adolescents that suggest that prior brain differences exist in a subpopulation of adolescents, perhaps making them more susceptible to developing depression in adolescence. No clear-cut neural indices were found that could usefully aid the evaluation of treatment response or clinical progress. Resting state functional connectivity may be the marker we currently have that is sensitive to change in these treatments.

Cortisol and Treatment Response

The third substudy investigated the relationship between both morning and evening baseline salivary cortisol levels and response to psychological therapies.[27] Only around 55% of the participants invited to give saliva samples provided valid samples for analysis, making the results preliminary. Prior research had suggested that elevated cortisol may contribute to slow treatment response.[46] This appears likely for evening rather than morning cortisol levels.[47] In this study, higher pre-treatment evening cortisol only was confirmed as being associated with a slower time to treatment response, regardless of treatment type, but did not predict final clinical outcome. These effects may be due to illness-related loss of diurnal variation and "escape" of the evening cortisol levels from impaired negative feedback. Functionally, higher evening cortisol may be associated with reduced motivation, accounting for the slower time to treatment response.[48] Establishing a laboratory standard for cortisol levels and noting the threshold for what constitutes a clinically meaningful elevated level would be worthwhile and of potential benefit to clinical practice.

WHAT WE LEARNED ABOUT THE THERAPEUTIC PROCESS OF PSYCHOLOGICAL TREATMENTS

All treatment sessions were audio-recorded, and a series of studies based on these data, together with the qualitative analysis of the IMPACT-ME semi-structured interviews with adolescents, their parents, and therapists examined the therapeutic processes across the 3 treatments (including the modality-specific studies of treatment process in IMPACT, which is beyond the scope of this review).

Treatment Expectations

Before treatment began, expectations about treatment pre-randomization revealed that participants often seemed anxious and uncertain, both about what therapy would be like and what they hoped to get from treatment.[49-51] Most saw therapy primarily as a "space" in which talking would predominate. This may sound obvious, but there was an over-riding sense that talking was how people understand themselves and others, and that it was through talking that change could take place. For many, this talking was part of a rather "medical" vision of therapy, in which participants imagined that a doctor-like figure would ask questions, diagnose, and treat their "disorder," offering advice or solutions that they would then follow. For a smaller number of adolescents, therapy was imagined more as a new relationship, in which talking and listening (or being listened to) were equally significant, and in which the therapist could facilitate a process in which the adolescents themselves began to find ways to change. For these adolescents, therapy was imagined in advance as an opportunity to develop new capacities or skills, rather than as a setting in which the problem would be "treated" and "cured."

Treatment Fidelity

The primary purpose of audio-recording the treatment tapes was to examine whether therapists delivered their respective treatments "on model." A random sample of audio-recorded therapy sessions in the trial were rated using the Comparative Psychotherapy Process Scale[52] to assess treatment fidelity of CBT and STPP. An absence of significant use of psychodynamic and/or cognitive–behavioral techniques was considered to be an indication that BPI was not based primarily on either of these approaches. Although the number of sessions delivered was lower than planned, within those sessions we found a high level of fidelity to the treatment models used by therapists in the STPP and CBT arms, with 80% of STPP and 74% of CBT sessions rated as adherent to their respective models, although the use of techniques based on the respective techniques was rated on

average as only "somewhat characteristic" of the sessions. These CBT and STPP sessions were clearly differentiated from BPI sessions.[53] A separate fidelity measure for BPI suggested that 81% of sessions were delivered "on model."[24]

When examining shared and unique techniques across the 3 treatment arms, 3 techniques (all considered on the CPPS to be part of the "psychodynamic–interpersonal" subscale) were found to be common across STPP, CBT, and BPI (albeit more frequent in STPP). These were as follows: the therapist encouraging patients to experience and express their feelings; the therapist suggesting alternative ways to understand experiences of events; and the therapist allowing the patient to initiate the discussion of significant events. These techniques are consistent with the CBT manual developed for the IMPACT study, and suggest that the CPPS items derived from published studies of STPP and CBT prior to 2005 may not fully reflect contemporary CBT practice. Other techniques were more specific to therapy models, with greater overlap between CBT and BPI than between STPP and the other 2 treatments.[53] Although significantly distinct, BPI therapists tended to use more cognitive–behavioral techniques than STPP. These included using a "teacher-like" manner with the adolescent whereby the therapist would actively initiate topics of discussion, encourage therapeutic activities and provide psychoeducation.

To provide another perspective on the therapeutic process, a set of CBT and STPP audio-recordings were also rated using the Adolescent Psychotherapy Q-Sort (APQ),[54] a measure of psychotherapy process. Results showed that when there was a collaborative working relationship between a therapist and adolescent, the therapy process in both types of therapy was highly influenced by the therapist's techniques, consistent with their treatment model (ie, STPP or CBT). However, when there was a poor working relationship with an adolescent not engaged in the session, the techniques used were more similar (eg, more structured and directive), regardless of the therapeutic modality, supporting the idea that therapists may drift from their therapeutic modality to try to work with a disengaged adolescent.[55] Although such drift may be appropriate and skillful, this drift also highlights that routine and frequent clinical supervision is an essential component of psychological therapy services.

Treatment Alliance and Therapeutic Relationship

The therapeutic alliance was measured using the Working Alliance Inventory (WAI), which is based on a conceptualization of the therapeutic alliance as comprising the bond and agreement on tasks and goals in therapy.[56] Adolescents reported the working alliance at 6, 12, and 36 weeks, and this was used to compare alliance trajectories across the 3 treatment arms (n = 338).[57] Adolescents who received CBT and BPI, on average, had a reasonably stable, moderately high alliance with their therapists. Adolescents who received STPP had lower initial alliance scores but showed a greater increase in alliance over time. In CBT, the therapeutic alliance was positively associated with outcome; this was not the case in BPI. This study suggests that in CBT, the emphasis placed on explicitly discussing goals and tasks for therapy may help to build a stronger alliance early in treatment. STPP focuses on establishing a secure base while allowing negative feelings to enter the relationship. This attention to negative feelings, along with the relative lack of explicit focus in STPP on the discussion of treatment tasks and goals, may explain the lower alliance scores earlier in treatment for adolescents who received STPP compared with BPI and CBT, despite similar treatment outcomes. By contrast, BPI focuses initially on psychoeducation, and the early use of an understanding mental states model may not require the formation of a strong alliance.[58]

Adolescents' narrative descriptions of their experiences of the therapeutic relationship among those who had good outcomes from CBT[59] suggested that therapist expertise and friendliness enabled adolescents to gain autonomy and to actively participate in their treatment. Despite the lack of association between self-reported alliance and outcome in BPI, the role of the therapist as an active participant was also important for adolescents with good outcomes in the BPI arm, with adolescents experiencing their therapists as being curious, using active listening, and having awareness of the adolescents' affective state.[60] The therapeutic relationship was also reported to be important for adolescents in STPP, with the therapeutic impact of "being heard and working together" identified as especially important.[61,62] Although adolescents emphasized the importance of the quality of the therapeutic relationship across all treatment types, focusing on the relationship between the therapist and adolescent was more prevalent in STPP than in CBT or BPI.[53]

Treatment Engagement and Dropout

In the IMPACT trial, 10.4% of participants did not take up the treatment on offer (ie, they attended no sessions) and 37.3% dropped out (defined as ending treatment without the agreement of their therapist).[63] Although dropout typically occurred in the early part of treatment and was predicted by early missed sessions, there were 3 pre-treatment predictors of dropout: older age, anti-social behavior, and lower scores of verbal intelligence.[63,64] There was, however, no strong evidence for a difference

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in long-term clinical outcomes for those adolescents who dropped out of treatment compared with those who completed pre-planned treatment.[64]

Given the unexpected finding that treatment dropout was not associated with poorer outcomes, further investigation was conducted to explore whether there was a more meaningful way of categorizing dropout, drawing on interview data from adolescent–therapist dyads.[32] Using ideal type analysis,[64] 3 types of dropouts were identified: "dissatisfied," "got what they needed," and "troubled." Dissatisfied dropouts reported finding therapy unhelpful, yet their therapists were often not aware of these adolescents' criticisms. "Got what they needed" dropouts reported positive change in their life and did not perceive a need to continue in treatment, and even if they saw benefits in the young person continuing, their therapists typically were not concerned about the young person's decision to end treatment. "Troubled" dropouts stopped attending primarily because of external factors that caused instability in their lives, rather than because of factors within the treatment itself. There was some indication that ending therapy as a "dissatisfied" dropout was associated with poorer outcomes, whereas "got what they needed" dropouts had equivalent (if not better) outcomes than treatment completers.

Ruptures and repairs in the therapeutic relationship with those adolescents who dropped out of therapy were also examined.[65] More ruptures were observed in early sessions with dissatisfied dropouts than for completers and "got-what-they needed" dropouts. For "dissatisfied dropouts," therapists were observed as having contributed more to the ruptures, and these ruptures were more often unresolved, than for the other groups. Qualitative analysis of therapy sessions enabled researchers to categorize 3 types of therapist contributions to unresolved ruptures of the therapeutic alliance: therapist minimal response, persisting with a therapeutic activity, and focus on risk.[65] By contrast, when therapists invited the young person's thoughts and feelings about the rupture, or recognized and acknowledged their own contribution to it, this was associated with a higher level of rupture resolution.[66]

Parents' Experiences of Managing Their Children's Depression and Treatment

As parental perspectives are often overlooked, we explored the experience of parents of depressed adolescents in the IMPACT study over time, including at pre-treatment, post-treatment, and 1-year follow-up. Using ideal type analysis, 3 distinct types or patterns of parental experience were identified: the "learning curve" parents (who made most use of the parental support offered), the "finding my own solutions" parents, and the "stuck" parents, whose experience parallels the "dissatisfied" dropouts described above.[67] These patterns of parental experience provide a basis for counselors and psychotherapists working therapeutically with adolescents to reflect on the families that they see and to adapt their ways of working accordingly to best support these families. In a further study exploring the experience of parents whose children received CBT,[68] parents perceived their adolescent child's readiness for therapy and the relationship between the therapist and adolescent as key factors that affected their therapeutic progress. Parents appeared to welcome increased communication between themselves and therapists. This indicates the importance of including parents in treatment planning with depressed adolescents, the potential value of psychoeducational resources for parents to help them to assess their understanding of their child's experience and treatment, and support from the therapist to help promote helpful parent understanding and behaviors at home.

SUMMARY, ISSUES, AND PROSPECTS

The primary IMPACT findings confirm that a major depressive episode can be effectively treated with 1 (at least) of 3, relatively short-term psychological interventions each as effective as the other. The study also highlights some of the challenges of delivering psychological therapies for adolescents with depression, including identifying depression, engaging adolescents and building a therapeutic alliance, supporting parents, following a treatment protocol, and managing drop-out.

Post-treatment longitudinal data show, for the first time, that the potential effects of psychotherapies appear likely to continue, or even continue to improve, for the 12 months following the end of treatment. Encouragingly, there is a good probability that the majority (around 84%) of adolescents report substantial reductions in their depression symptoms. Furthermore, health service use assessments over the 12-month follow up period noted that less than 1% of participants subsequently returned to mental health services and that between 2% and 4% received additional medications (psychotropics or others not associated with known medical conditions). The latter data were collected on only 66% of the participants and are therefore to be read with caution. Encouragingly, although treatments were developed for depression, their impact was demonstrated on a wide range of outcomes including symptoms of anxiety, obsessive-compulsive disorder, behavior problems, and functioning. The treatments were both transdiagnostic and trans-symptomatic in their effects,

and therefore improvements in global well-being in responders is highly likely from these findings. Similar transdiagnostic and trans-symptomatic positive responses were identified from the TADS and the ADAPT studies.[69,70] Thus, a range of time-limited psychological interventions are an effective response to adolescent depression and its comorbidities.

However, at the same time, these overall patterns may hide significant heterogeneity, in terms of both the experience underlying mechanisms of depression and the treatment response. The identification of a subgroup of adolescents (ie, the "halted-improvers") with higher depression severity and comorbidity at baseline suggests that it is important to identify adolescents who are less likely to respond to a short-term psychological intervention, although they may initially show some improvement. Likewise, identifying adolescents who might have features of the "troubled dropouts"—even before treatment begins—could highlight the need for greater focus on engagement and on careful assessment and case formulation, supported by regular clinical supervision for therapists.

The findings are the first to note the clinical equivalence of 3 distinctive psychological therapies in this depressed adolescent cohort, but this is not new in itself: similar observations have been made in studies of depressed adults.[71] The implications for adolescents are that beyond CBT, both STPP and BPI are valid additional treatments for depressed youth: a conclusion that has been supported by the most recent clinical guidance on the treatment of child and adolescent depression in the United Kingdom, developed by the National Institute for Health and Care Excellence.[72] STPP is a well-established therapeutic approach with a treatment manual for treatment of adolescent depression.[16] The methods of treatment in BPI are easily teachable to existing mental health practitioners, and there is now a training program operating in the United Kingdom, United States, and Canada via video learning and online ongoing supervisions (for more details, see https://www.cambridgebpi.com and Goodyer and Kelvin[58]). Indeed, from the clinical practice and service delivery perspective, we suggest that, regardless of therapy type or therapist orientation, it is possible that briefer therapies can be "prescribed" more than often have been so far, at least for some depressed adolescents. However, consistent with wider findings highlighted in the review by Eckshtain *et al.*,[9] the effect sizes of psychological therapies for depression in adolescents overall are modest and have remained so over time. It is also consistent with the comprehensive meta-analysis by Cuijpers *et al.*,[73] which found that across 37 studies in children and adolescents, which compared participants receiving CBT to control groups, there was a pooled moderate effect (g = 0.41; 95% CI = 0.25-0.57). As Thapar *et al.*[74] suggest, this is likely to reflect the fact that depression is highly heterogeneous, indicating a need for a greater focus on assessment and personalized treatment planning, along with a better understanding of the mechanisms of change.

The IMPACT study provided an opportunity to examine some key elements of psychological therapies. For example, the assumption that therapy works only through the emergence of a strong therapeutic alliance was not fully supported; in BPI, the strength of the alliance did not predict outcome. However, in semi-structured interviews, adolescents consistently emphasized the importance of the therapeutic relationship. Adolescents' accounts, along with study of therapy transcripts, suggest that the way in which therapists respond to the inevitable ruptures in the therapeutic relationship might be more important than a global rating of the overall alliance *per se*.[66] Likewise, identifying and actively exploring early signs of treatment dissatisfaction, including sporadic attendance and withdrawal ruptures (which may easily go undetected) could lead to better treatment engagement.[32] The importance of understanding Q7 the therapeutic mechanisms more effectively in order to develop personalized and precision psychotherapies is suggested from these results. This can be examined both through quantitative analysis of treatment moderators and also qualitatively. The adolescent experience findings have confirmed the possibility of expectation and therapy experience as moderating and mediating treatment response. These types of qualitative assessment should be incorporated in future trials and studies of the effects of treatment over time.

Findings regarding participants who dropped out of therapy raise questions about how different types of treatment endings may be managed. The "got-what-they-needed" dropout type suggests that for some adolescents, a brief intervention may be enough, and therapists could allow adolescents greater control over deciding when to end therapy, even if there has been the intention for a longer-term intervention. For "dissatisfied" dropouts, there may be observable interactions (ie, withdrawal ruptures and showing subtle signs of dissatisfaction) that could be identified early in treatment. Training practitioners in recognizing and managing such ruptures may go some way in making therapies more acceptable for adolescents who may end treatment for negative reasons. Perhaps most urgently at risk and in need of support are the "troubled" dropouts. These adolescents may require more support from services to attend sessions and to engage in their sessions, and may face complex or adverse socioeconomic difficulties that may place them at further risk for adverse

outcomes. It is important that services be able identify these adolescents before offering out-patient therapy, so that therapists can increase support or can refer the adolescent to more easily accessible support such as assertive outreach programs, school mental health practitioners, or additional services.

Several limitations of the IMPACT study mean that some clinical implications must be treated with caution. Although the use of SSRI medication was not associated with any differences in outcome among treatment arms, it is unclear how medication contributed to outcomes, or whether guidelines for use of medication were followed appropriately. Prior studies have noted that adding a CBT modality for individuals on fluoxetine can reduce relapse risk.[75] Whether the reverse is also true remains to be fully evaluated. The IMPACT follow-up period was also too short to definitively address factors associated with the known high recurrence risk rate in the years following the remission from first episode of depression. Biological markers of treatment moderation deserve a more detailed examination from the preliminary investigations noted from IMPACT. Behavioral phenotype investigation confirms the high likelihood of clinically meaningful subtypes with differing trajectories over time. These need further investigation with a planned *a priori* objective of determining whether clinical subtypes index different treatment needs and predict variations in therapy response. Imaging markers for treatment response may be aided by the recent publication of brain charts reporting robust quantification of individual variation benchmarked to normative trajectories.[76]

From the clinical and public health perspective, the findings of this study support a psychological therapy approach as a reasonable first-line treatment for major depression in adolescents presenting to mental health services. The role of fluoxetine as a potential first-line therapy is established through other trials with more cogent pharmacology designs. This conclusion is in line with clinical guidelines in the United Kingdom but differs from the conclusion drawn by Zhou *et al.*[77] in their network meta-analysis examining the comparative efficacy of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder. In this review, Zhou *et al.*[77] concluded that "fluoxetine (alone or in combination with CBT) seems to be the best choice for the acute treatment of moderate-to-severe depressive disorder in children and adolescents" (p. 581). However, as Leichsenring *et al.*[78] point out, 100% of the comparisons for efficacy in this network analysis were reported as being of low or very low confidence; and, as such, the authors argue that "no conclusions from the network meta-analysis can currently be drawn with confidence regarding the treatment of young people with depression" (p. 96).

What is clear is that not all young people will be helped by a time-limited psychological therapy. There was also a clear non-responder group in IMPACT across all treatments, including those participants who received combined psychotherapy and fluoxetine, of some 16% to 18% depending on the precise type of measurement. Further research into the difficult-to-treat depressed adolescents is an urgent priority. We suggest that, to disentangle what works for whom and to personalize interventions more than done so far, adaptive sequential step-wedge effectiveness design trials should replace pragmatic parallel trial designs, examining both psychosocial and pharmacological treatments. These approaches may be the next step in helping practitioners in determining what works for whom and policy makers in deciding how best to design and cost healthcare services for depressed adolescents.

Accepted April 21, 2023.

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Dr. Loades (Development and Skills Enhancement Award, 302367) is funded by the National Institute for Health Research (NIHR) for this research project. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS, or the UK Department of Health and Social Care. None of the other authors received any funding for work on this manuscript. The Improving Mood With Psychoanalytic and Cognitive Therapies (IMPACT) study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 06/05/01). The IMPACT-ME study was funded by the Monument Trust. The IMPACT-MR study was funded by a Medical Research Council award (grant no: G0802226). This report is independent research. The views expressed in this publication are those of the authors(s) and not necessarily those of the HTA programme, NHS, the Monument Trust, the National Institute for Health Research, or the Department of Health. The IMPACT trial is registered under Current Controlled Trials: ISRCTN83033550.

Author Contributions
NM, IMG, SR, and the IMPACT Consortium designed and conducted the IMPACT study. IMG designed and co-led the imaging work, embedded within the IMPACT trial, and NM designed and led the qualitative sub-study, IMPACT-My Experience. ML and NM wrote the first draft of the manuscript with input from SO'K, GH, IG, and SR. All authors contributed to and approved the final manuscript.

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Disclosure: Prof. Reynolds is a company director for CBTReach Ltd. and has received fees for training and teaching CBT for adolescents. Between April 2021 and January 2023, she was employed by the British Association of Behavioural and Cognitive Psychotherapies. Prof. Goodyer is a company director of CambridgeBPI Ltd. and has received fees for teaching and training BPI. Dr. Loades, Prof. Midgley, Dr. O'Keeffe, and Ms. Herring have reported no biomedical financial interests or potential conflicts of interest.

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https://doi.org/10.1016/j.jaac.2023.03.017

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