Emotional Regulation In Teens And Improvement of Constructive Skills (EmoTIConS): Study Protocol For A Randomized Controlled Trial

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Study protocol

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Abstract

Background: Emotional dysregulation (ED) constitutes a relevant factor involved in the onset and maintenance of many mental disorders. Targeting ED during adolescence could be determinant both to identify high risk individuals and to promote preventive interventions. This study will aim to evaluate the impact of a brief Dialectical Behavioral Therapy (DBT)-based intervention for adolescent students by measuring changes in emotional regulation skills and impulsive behaviors. Moreover, alterations in biological features related to stress response and inflammation will be assessed as potential biological variables associated to ED.

Methods: This is a randomized trial. A total of 20 classes of adolescent students will be recruited among high schools in Brescia, a city in the North of Italy. They will be randomized to the psychoeducational intervention (experimental group) or to a control condition (control group). The intervention will be based on DBT Skills Training for Emotional Problem Solving for Adolescents, and it will consist in four monthly 2-hours sessions (for a total of 8 hours) scheduled during regular school-time. Participants will be assessed at baseline, post-intervention, and at 3 and 6-month of follow-up. The primary outcome measures will be represented by changes in the use of emotional regulation skills (measured by the DBT-Ways of Coping Checklist) and by changes in the frequency of impulsive behaviours (measured by an ad-hoc created checklist). Salivary samples will be collected at baseline and post-intervention to explore possible biological features underlying ED.

Discussion: Data from the present project will offer the opportunity to better understand the complex phenomenon of ED. Repeated assessment will cover several domains (emotional, behavioral, social, biological) as potential factors associated with ED. Moreover, it will be possible to measure the effect of the proposed intervention, contributing to improve knowledge on the impact of school-based universal preventive programs. Finally, the current trial will propose an integrated screening- and intervention-based model. Ultimately, this could reduce barriers to youth's mental health care by fostering collaboration between schools and mental health services.

Trial registration: ClinicalTrials.gov ID: NCT04349709. Registration date: 16/04/2020

https://clinicaltrials.gov/ct2/show/NCT04349709

Introduction

Background and rationale {6a}

Adolescence is a critical period since most of the mental disorders develop before the age of 25 years (1). The Health Behaviour in School-aged Children (HBSC) study prospectively assessed several aspects of physical and psychological well-being of adolescent students from different countries (2). Findings from HBSC showed a small linear increasing trend in psychological distress indexes, especially in higher

income countries (3). Of note, compared to other countries, Italy reports the highest rate of youths that refer sadness, irritability, sleep problems, and psychosomatic health complaints (3).

The ability to regulate emotions represents a determinant variable and it is strictly associated with the mechanisms involved in pursuing personal goals and to establish positive interpersonal relationships (4). Of note, difficulties in emotional regulation processes represent a relevant risk-factor for the development of mental disorders (5, 6). Emotional dysregulation (ED) is a multidimensional construct including different facets, such as lack of awareness about experienced emotions, non-acceptance of emotional distress, impulsivity, inability to pursue goals when emotionally distressed, and lack of regulatory strategies (4). ED represents the core dimension of Borderline Personality Disorder that is mainly characterized by rapid and intense emotional changes, impulsive behaviors, and unstable relationships (7). Reduced abilities in regulating emotions represent a relevant feature that can be observed also in other mental disorders such as depression and anxiety (8, 9) and with other clinical conditions, such as substance-related problems (10, 11), suicidal ideation (12), and self-harm (13). Indeed, in the absence of more adaptive coping mechanisms, health-risk behaviors (e.g. self-harm, alcohol or substance abuse, risky sexual behaviors etc) are sometimes used to manage psychological distress (14, 15).

Since emotional regulation is a modifiable skill, interventions helping students to improve emotional regulation related strategies could represent a promising primary prevention approach. Several evidences support the use of Socio-Emotional Learning (SEL) as part of school educational programs (16, 17). SEL programs are aimed to help children and adolescents to acquire and practice the skills they need for successfully mastering stressful life events (16, 17). A meta-analysis about SEL programs found that children and adolescents that participated in SEL programs showed better indicators of social-emotional skills and well-being compared to those that did not participated (18). Adolescence is characterized by high emotional stress because of demands that typically occur in this period such as academic pressure, dating and intimacy issues, bullying, peer rejection, alcohol and drug use, concerns about physical attractiveness, and becoming more independent of parents. Therefore, adolescents may have particular need to regulate their emotion to face with stressors and to carry out crucial steps involved in the formation of their identity and personality (19).

Emotion regulation abilities develop substantially during adolescence, shifting from the reliance on parental support to internal regulatory processes (20), and this change parallels the neurobiological changes in brain circuits involved in emotional process (21). It is well known that early traumatic experiences and stressful life events are strong risk factors for the onset of mental disorders (22) and individuals exposed to early traumatic experiences exhibit difficulties in regulating their emotional responses (23). Among the biological systems involved in the effect of stressful experiences on the vulnerability to develop ED and more in general psychiatric disorders there is the hypothalamic-pituitary-adrenal (HPA) axis (24–26). More in details, the exposure to early stressful life events may cause persistent alterations in the HPA axis functionality leading to a persistent release of the stress hormone cortisol. Cortisol acts on its receptors, that are widely distributed in limbic brain regions, thus influencing stress response, cognition, affect, and behavior (24). In line with this, in a sample of 180 adolescents at

high risk for psychopathology, it has been found that high morning cortisol levels predicted the onset of a major depressive episode in the following year (27). Another similar study showed that high morning saliva cortisol levels predicted in 13-year-old adolescents the development of depressive symptoms at the age 16 (28). However, although the presence of alterations in cortisol release and depression is well established, weaker are the findings in the context of anxiety disorder or externalizing disorder. Indeed, some authors did not found association between cortisol and psychopathology, or they found association in a different direction than expected (29, 30). The age and severity of symptoms constitute relevant factors for HPA axis functioning, thus contributing to explain the inconsistencies in available evidence (29). Moreover, the majority of the studies included adults.

Investigations with adolescents are needed to understand the exact nature of the relation between HPA axis and psychopathology. In this framework, the identification of biological variables linked to difficulties in emotional regulation in youths had been recognized a relevant domain in order to identify possible factors of susceptibility for mental disorders (31).

Objectives {7}

The aim of the present study is twofold. The first aim is to evaluate the impact of a school-based intervention focused on emotional regulation strategies in a sample of adolescent students. Primary outcome will be represented by changes in the frequency of use of emotional regulation skills (assessed with the DBT-Ways of Coping Checklist (32), and changes in the frequency of impulsive behaviors (assessed with the Checklist for Impulsive Behaviors). Our hypothesis is that: 1) at the end of intervention, the students who received the intervention will report a reduction in the frequency of impulsive behaviors as compared to baseline, whereas we do expect no differences in the group of adolescents that will not receive the intervention; 2) at the end of intervention, the students will report increase in the use of emotional regulation skills compared to baseline; while we expect no differences in the control group 3) these changes will be maintained after 3 and 6-month follow-up.

The second aim of the study is to assess the association between biological features and ED in adolescent students. Precisely, we will compare several biomarkers related to stress response and inflammation in subgroups of students with different level of ED (assessed with the Difficulties in Emotion Regulation Scale (4)) measured at baseline. Moreover, the repeated collection of salivary samples at post-intervention will allow to evaluate the role of these biological features also in the effects of the interventions on the behavioral variables described above (i.e. impulsive behaviors and use of skills).

Trial design {8}

This is a randomized trial. The classes of students will be randomized into a psychoeducational intervention (experimental group) or control condition (control group). All the participants will be assessed at baseline, post-intervention, and at 3 and 6-month follow-up by using self-report

questionnaires. In addition, salivary samples will be collected at baseline and post-intervention. Details on the timeline and the assessments are reported in Table 1.

Table 1. Timeline and assessments of the study

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				
TIMEPOINT			*Baseline*	*End-intervention*	*Post-intervention*	*3month follow-up*	*6month follow-up*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
[experimental: Psychoeducation]			◆—	—◆			
[control: no intervention]			◆—	—◆			
CLINICAL ASSESSMENTS:							
Impulsive Behavior (CIB)			X		X	X	X
Skills (DBT-WCCL)			X		X	X	X
Problem-solving (SPSI-R:SF)			X		X	X	X
Emotional dysregulation (DERS)			X		X	X	X
Depression (PHQ-9)			X		X	X	X
Anxiety (SCARED)			X		X	X	X
Personality traits (PID5)			X				
Impulsivity (BIS)			X				
Childhood trauma (CTQ)			X				
Stressful life events (ASQ)			X				
School climate (SCM)			X				
Classmate relations (CASS)			X				
Family functioning (FAD)			X				
BIOLOGICAL ASSESSMENT							
Salivary sample collection			X		X		

CIB *Checklist of Impulsive Behaviors;* ***DBT-WCCL*** *DBT-Ways of Coping Checklist (DBT-WCCL) (32);* ***SPSI-R:SF*** *Social Problem-Solving Inventory-Revised Short Form (36); DERS Difficulties in Emotion Regulation Scale (4);* ***PHQ-9*** *Patient Health Questionnaire (40);* ***SCARED*** *Screen for Child Anxiety Related Emotional Disorders (41);* ***PID5*** *(Personality Inventory for DSM-5 (44);* ***BIS-Brief*** *Barratt Impulsiveness Scale–Brief (43);* ***CTQ*** *Childhood Trauma Questionnaire (45);* ***ASQ*** *Adolescent Stress Questionnaire (46);* ***SCM*** *School Climate Measure (47);* ***CASS*** *Child and Adolescent Social Support Scale (48);* ***FAD*** *Family Assessment Device (49).*

The present study protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (33) and a copy of the SPIRIT Checklist is included in the Additional file 1.

Methods: Participants, Interventions And Outcomes

Study setting {9}

A total of 20 school classes will be recruited among the high-schools of Brescia (Northern Italy), for a total of about 440–460 students (considering about 22–23 students per school class) attending several high-schools. Each school will enrol an even number of classes to be randomized to experimental or control condition.

Eligibility criteria {10}

The inclusion criteria will be: age 16–19 years; to attend the third year of high-school (10th academic grade); signed informed consent. Exclusion criteria will be: a certified diagnosis of mental retardation, or of autism spectrum disorders. All the students will fulfil the assessment questionnaires and they will participate to the project activities.

Who will take informed consent? {26a}

The participation in the study will be voluntary and the participants will be allowed to withdraw their involvement in the study at any time. Teachers and project staff members will organize meetings with parents and students to introduce the study and to answer their questions. Project staff members will ask to both students and parents to sign the consent form. Information sheets and consent forms – both for parents and for students - have been approved by the local ethical committee, the Comitato Etico IRCCS Fatebenefratelli.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

No ancillary studies

Interventions

Explanation for the choice of comparators {6b}

The classes randomized to control group will not receive any intervention.

Intervention description {11a}

The psychoeducational intervention will be based on DBT Skills Training for Emotional Problem Solving for Adolescents (DBT STEPS-A), a manualized program designed to help adolescent students to develop

coping strategies and decision-making abilities, especially under emotional distress (34). The DBT STEPS-A covers all four primary skill modules of the DBT skill training (Mindfulness, Distress Tolerance, Emotion Regulation, and Interpersonal Effectiveness). The DBT STEPS-A program has been conceived in the US context to be delivered as a universal social–emotional learning curriculum and it consists in approximately 30 weekly lessons organized into 50-minute blocks.

For the present trial, we selected within the original DBT STEPS-A the specific elements related to ED. The intervention will consist in four sessions of 2 hours each per month (for a total of 8 hours) scheduled during regular school-time. The details of each session are reported in Table 2. Sessions will be conducted by two psychotherapists (a leader and a co-leader) who have attended specific trainings on DBT (27) and DBT-A (35).

Table 2. Description of the intervention.

* The handouts were taken from the Italian version of the of Mazza et al., (2016) (34).

Active participation of students will be encouraged, and, at the end of each session the key-concepts will be written on a poster hanging in the classroom as reminder. Homework will be also assigned in order to practice the learned skills in real environment and will be reviewed at the beginning of the following session.

Criteria for discontinuing or modifying allocated interventions {11b}

We did not planned to modify allocation.

Strategies to improve adherence to interventions {11c}

All the activities of the study will be scheduled during regular school-time according to academic planning in order to facilitate the attendance of the students.

The contents of the psychoeducational intervention will be structured. The fidelity to the intervention will be supported by regular meetings of the project team. Team meetings will be scheduled weekly in a pre-study phase, and then they will be scheduled monthly. For each session of the psychoeducational intervention, the co-leader will fulfil a checklist to register the contents of the session and to record the attendance of students.

Adherence to the procedure for salivary sample collection will be promoted by phone alert messages at established hours and by written reminders about the exact procedure.

Relevant concomitant care permitted or prohibited during the trial {11d}

Concomitant care will be permitted.

	Aims	Contents and skills	Methods*
Session 1 (2 hours)	1. To describe goals of emotional regulation and function of emotions 2. To enhance emotional literacy	• Emotional dysregulation and emotional regulation skills. • Levels of emotion chart • The concept of biological vulnerability • The functions of emotions • Homework: to describe emotional events through the ABC (Antecedents, Beliefs, Consequences) diary.	- Slideshow - Handouts 15.1, 15.3 - Class exercices
Session 2 (2 hours)	1. To practice with the model of emotions 2. To gain the skills to manage interpretations and impulses to action.	• The model of emotions: emotion is a complex response made up of different components (prompting event, interpretation, biological changes, expressions, and aftereffects). • Emotion are set off by our interpretation, not by the events themselves: the skill “Check the facts” • Emotion have an action urge, by changing behavior, we can change emotion: the skill “Opposite action” • Homework: practice with check the facts and opposite action	- Slideshow - Role-playing - Handouts 16.1-2, 17.2-4 - Class exercises
Session 3 (2 hours)	1) To improve strategies to solve a problem 2) To learn how to accumulate positive emotions.	• How to solve a problem: the seven steps of problem-solving • Accumulate positive experiences in the short term: the skills “pleasant activities” and “building mastery”. • Accumulate positive experiences in the long term: identifying personal values and plan goals. • Vulnerability factors and the PLEASE skills • Homework: practice with AB Please	- Slideshow - Handouts 18.1, 19.2-5, 20.1-4 - exercises in small groups
Session 4 (2 hours)	1) To learn how to reduce intense emotion quickly in order to avoid impulsivity	• The autonomic nervous system and the “fight-or-flight” reaction • Activate parasympathetic system by reducing body temperature, using intense exercise, and engaging in paced breathing: the TIPP skills. • Homework: practice with TIPP skills	- Slideshow - Handouts 6.2, 8.1. - Classes exercices.

Provisions for post-trial care {30}

Not applicable.

Outcomes {12}

Primary outcomes

The primary outcome measures will be the change in the use of emotional regulation skills and the change in impulsive behaviors that will be measured by the following instruments, respectively:

DBT-Ways of Coping Checklist (DBT-WCCL) (32). The DBT-WCCL is a 59-item self-report questionnaire measuring the frequency of DBT skills use (DBT Skills Subscale, 38 items) and dysfunctional coping strategies (Dysfunctional Coping Subscale, 21 items). Participants will be asked to indicate on a 4-point Likert scale the frequency of use of each skill in the previous month (i.e. never used, rarely used, sometimes used, or regularly used). The scale showed good internal consistency (Cronbach's alpha coefficients for the subscales ranged from .84 to .96) and content validity (32).

Checklist for Impulsive Behaviors (CIB). This CIB is an ad-hoc created checklist to measure the frequency of impulsive behaviors: alcohol use (4 item), substance use (2 item), internet addiction (4 item), gambling (1 item), non-suicidal self-injury (2 item), unprotected sex (1 item), binge-eating (1 item). Participants will be asked to indicate on a 5-point Likert scale the frequency of impulsive behaviors occurred in the previous month (never; only one time; once a week; two or three times a week; at least 4 time a week). Moreover, lifetime frequency of each behavior will be assessed on a 6-point Likert sale (1–2 times, 3–5 times, 6–9 times, 10–19 times, 20–39 times, at least 40 times).

Secondary outcomes

The secondary outcome will be represented by changes in problem-solving strategies, ED, symptoms of depression, anxiety, and impulsivity, measured by the following instruments:

Social Problem-Solving Inventory-Revised Short Form (SPSI-R:SF) (36, 37). The SPSI-R:SF is a 25-item self-report questionnaire measuring the abilities in problem-solving: positive problem orientation (PPO), negative problem orientation (NPO), rational problem solving (RPS), impulsivity-carelessness style (ICS), avoidant style (AS). Each item is rated on a 5-point Likert scale and scores are computed for each of these subscales as well as a global score for the total inventory. Higher scores on the NPO, ICS and AS reflect a more maladaptive approach to problem-solving, whereas higher scores on the PPO and RPS indicate more adaptive strategies. Studies reported good construct validity, internal consistency (Cronbach's alpha coefficients ranged from .73 to .86) and test-retest reliability (Intraclass Correlations Coefficients ranged from .74 to .87) (36, 37).

Difficulties in Emotion Regulation Scale (DERS) (4, 38). The DERS is a 36-item self-report questionnaire measuring different dimensions of ED: non-acceptance of emotional responses; difficulties engaging in goal-directed behaviour; impulse control difficulties; lack of emotional awareness; limited access to emotion regulation strategies; lack of emotional clarity. Each item is rated on a 5-point Likert scale and scores are computed for each of these subscales as well as a global score for the total inventory. The

DERS represents the most comprehensive measure of ED to date, and it exhibits good reliability and validity when administered to adults (4). Specific analyses confirmed reliability and validity of the DERS also in adolescents (Cronbach's alpha coefficients ranged from .76 to .89 for the subscales) (39). The Italian version of the DERS showed adequate and comparable properties (38).

Patient Health Questionnaire-9 (PHQ-9) (40). The PHQ-9 is a 9-item self-report questionnaire measuring depression severity. Each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day) and a total score is computed as the sum of the nine items. Studies showed that the PHQ-9 has an excellent internal validity (Cronbach's alpha coefficient higher than .85), and test-retest reliability. Different level of severity of depression can be distinguished according to the cut-off (40).

Screen for Child Anxiety Related Emotional Disorders (SCARED) (41, 42). The SCARED is a 38-item self-report questionnaire measuring different manifestations of anxiety: panic disorder, generalized anxiety disorder, separation anxiety disorder, school anxiety, and social anxiety. The SCARED showed good internal consistency and test–retest reliability (41). The Italian version of the SCARED had been found a valid screening instrument (42).

Barratt Impulsiveness Scale–Brief (BIS-Brief) (43). The BIS-Brief is 8-items self-report questionnaire for the assessment of the personality construct of impulsiveness in adolescents (43). The BIS-Brief showed with good reliability and construct validity (43).

In addition, at baseline, the following instruments will be administered to assess psycho-social domains associated to ED: **Personality Inventory for DSM-5** (44) for personality traits; **Childhood Trauma Questionnaire** (45) for early adverse experiences; **Adolescent Stress Questionnaire** (46) for stressful life events in the previous year; **School Climate Measure** (47) for school-climate; **Child and Adolescent Social Support Scale** (48) for relationship with classmates; **Family Assessment Device** (49) for family functioning.

At the baseline, data on socio-demographics, contacts with mental health professionals, pharmacological treatments, lifestyle (sleep quality, free time activities, number of friends) and academic performance will be collected.

Participants' timeline {13}

Details about the timeline and the assessments are reported in Table 1.

Sample size {14}

The primary outcome measures will be represented by changes in impulsive behaviors (measured by the Checklist for Impulsive Behaviors) and by changes in emotional regulation skills (measured by the DBT-Ways of Coping Checklist).

Precisely, the outcome will be evaluated in terms of change (pre-post) in percentage of "yes" answers in the two groups (treated and control); where the "yes" answer is defined as a difference of at least one

category, toward improvement, from the baseline. More in details, the scores of the Checklist for Impulsive Behaviors are on a Likert scale, therefore a “yes” answer means a decrease of frequency of impulsive behavior for example from the category “two or three times a week” to the category “one time a week”. In a similar manner, a “yes” answer for the DBT-Ways of Coping Checklist means a decrease in use of dysfunctional skills for example from the category “regularly used” to “sometimes used”, or vice versa for functional skills.

We assumed that, at baseline, there will be a between groups difference by chance of 7% (i.e. 1/15 yes answers, -where 15 is the total number of checklist items-) on the Checklist for Impulsive Behaviors, and that this difference will increase up to 13% (i.e. 2/15 yes answers) after the intervention. Based on these assumptions and applying a two-sides test for paired binomial proportions with significance level equal to 0.05 and a power of 0.8, the estimated sample size was n = 340 (170 per group). Moreover, considering a drop-out rate of 20%, the minimum sample size (MSS) we reached an n = 426 (213 per group).

In the same way, we assumed that on the DBT-Ways of Coping Checklist there will be a difference by chance of 7% (i.e 4/59 yes answers, -where 59 is the total number of the checklist DBT items-) at baseline and that this difference will increase up to 20% (i.e. 12/59 yes answers) after the intervention. This last hypothesis has been made considering that, given the focus of treatment, we expect a higher change in emotional regulation skills than in dysfunctional behaviors. Based on these considerations and applying a two-sides test for paired binomial proportions with significance level equal to 0.05 and a power of 0.8, we reached an estimated sample size of n = 84 (42 per group).

In conclusion, considering both the outcome measures and related sample size estimations, the final sample size needed is of 426 students.

Recruitment {15}

The enrolment of the target sample size will be ensured by specific strategies based on loyalty. The research team draw upon already consolidated collaboration with several schools of the city. Moreover, all the students completing all assessments will be awarded with books or e-books.

Assignment of interventions: allocation

Sequence generation {16a}

After enrolment, the statistician will randomly assign the classes, within each school, to experimental or control condition. More in detail, a random sequence of strings (of length equal to the number of school classes) with labels “Experimental” or “Control” will be generated by a computer code, with a ratio -Experimental vs Control- of 1:1. The classes will be then linked to the random sequence following their alphabetic order.

Concealment mechanism {16b} and Implementation {16c}

Reported in 16a

Assignment of interventions: Blinding

Who will be blinded {17a}

Given the nature of the intervention neither the project psychologists nor the participants can be blinded for the intervention.

Procedure for unblinding if needed {17b}

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes {18a}

To enhance data validity, assessment sessions will be planned for each class of students at baseline, post-intervention, and at 3 and 6-month of follow-up. The researcher will remain available during the sessions to answer student' questions and to ensure that students will complete the questionnaires independently.

Plans to promote participants' retention and complete follow-up {18b}

To promote both the involvement in the evaluation and to make sure that each participant can complete the whole evaluation, all the activities will be planned in agreement with school personnel during the school time. Moreover, one or two teachers will be identified as the contact persons for each class.

Data management and storage {19}

Data will be registered into a digital database, that will be stored at the study site following procedures in line with privacy policies. In particular, after obtaining informed consent, each participant will be associated with an alphanumeric unique code, databases will be stored on a secure server and they will be protected by passwords. Only authorized research personnel will have access to the database.

Confidentiality {27}

Reported in Data management {19}

Workflow for collection, laboratory evaluation and storage of biological specimens for molecular analysis {33}

After completing the questionnaires, the researcher will explain the procedure to collect the salivary samples by OraGene tubes and Salivette that will be used to measure a panel of inflammatory mediators by Luminex technology. RNA samples from OraGene tubes will be isolated by using RNAesy Kits and RNA samples will be processed to have a gene expression profile by using the RNAseq technique on Illumina platform and data will be analysed to identify peripheral genes associated with ED. Tubes for the diurnal cortisol samples collection that will be carried out the next day (morning, afternoon, evening) will be also provided to each individual and saliva samples will be then analysed for cortisol levels by ELISA technique. Participant Information paper reporting all the detailed steps regarding the exact procedure to collect saliva sample for cortisol measurements will be provided. In this form there is also a dedicated space that can be used by the students to annotate the exact time of sample collection, and eventually, any problems that occurred during the saliva collection. The salivary samples will be used only for the purpose reported in this protocol.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Descriptive statistics (frequencies and percentages for categorical variables and means and standard deviations for continuous variables) will be evaluated. To compare categorical variables Chi-squared test will be used. To compare continuous variables between the different groups of interest t-test or ANOVA, or corresponding non-parametric tests (Mann-Whitney or Kruskal Wallis), will be performed- Moreover, generalized mixed models will be performed for assessing the differences in dysfunctional behaviors and emotional regulation skills across time and between groups.

Differences in the levels of the biomarkers will be assessed by using linear and generalized linear models adjusting for potential confounders such as gender. Correlations (Pearson or Spearman) and generalized linear models will be used to assess the association between the level of emotional dysregulation and other clinical variables and the biomarkers.

Interim analyses {21b}

Not applicable

Methods for additional analyses (e.g. subgroup analyses) {20b}

Not applicable

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

An evaluation of type of missing data will be performed in order to detect any missing not-at-random outcome data. In case of missing not-at random, or missing on outcomes of main interest, a subsequent data-imputation technique (Bayesian imputation performed in a context of Structural Equation Modeling technique) will be applied to obtain complete outcome data.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The protocol has been registered at ClinicalTrial.gov registry. The dataset collected during the current study will not be publicly available and data will be shared only upon reasonable requests that will be evaluated by the corresponding author.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

A formal steering committee has not been established.

Composition of the data monitoring committee, its role and reporting structure {21a}

A formal data monitoring committee has not been established.

Adverse event reporting and harms {22}

Not applicable.

Frequency and plans for auditing trial conduct {23}

Not applicable.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

A plan of period communication to ethical committee had been established

Dissemination plans {31a}

Results of the study will be presented at international scientific congresses and published on international scientific journals.

Discussion

ED is a relevant factor involved in the onset and in the maintenance of many mental disorders (50). For this reason, interventions focused on this construct are particularly useful during adolescence, that is a temporal window of vulnerability, for the development of mental illnesses. Moreover, it is well recognized that school represent the elective setting to promote youths' mental health (51, 52) and to reduce barriers to youth mental health care.

The main aim of the present trial is to evaluate the effect of a DBT-based intervention in a sample of adolescent students. DBT is an empirically supported treatment based on the biosocial theory of ED (53). The common underlying dysfunction in emotion regulation makes this treatment a valid transdiagnostic approach in the clinical settings (54). DBT was originally conceived for adults with Borderline Personality Disorder, and subsequently this treatment has been adapted for adults with different psychiatric conditions (55–57), as well as for adolescent patients (58–60). DBT skills represent basic social and emotional life skills, indeed they are useful for everyone and they have been found useful also in non-clinical population, such as school contexts (61), and DBT-STEPS-A is the adaptation of DBT specifically designed for students of middle and high school age.

Studies evaluating the efficacy of DBT-STEPS-A are still ongoing, however preliminary data suggest that the students show reductions in emotional distress after the first year of intervention (62). In a sample of 8th grade students receiving the first two modules of the DBT STEPS-A modules (Mindfulness and Distress Tolerance), most of the participants declared that they would use the skills themselves and they thought that the skills would be useful also for others (63). In this context and considering these preliminary data, the present trial will contribute to further evidence on the use of an intervention with strong theoretical foundation also in a school setting in Italy. This is particularly relevant since, to our knowledge, outside United States, there is only one project from Ireland which apply DBT-STEPS-A (64).

It should be noted that for the present trial we will include in the intervention only some of the skills of the DBT-STEPS-A program. Our choice was based on the consideration that the full 30-lessons based program could be applicable only as an optional-choice course. Therefore, in order to avoid self-selection bias and to be in line with a primary prevention approach, we preferred a shortened version of the program to be delivered to all the students. Our purpose is also to collect evidence on the feasibility and outcome of DBT-based interventions within school environment, as well as to spread knowledge and awareness on mental health among teachers. In a recent study in Ireland (64), the authors reduced the length of the program (from 30 to 22 lessons) to adapt it to an Irish school context, however schools faced challenges in delivering the programme as only 2 out of 8 of the participants covered the entire program (65). Although our intervention does not cover the entire DBT-STEPS- A, it could be a valid strategy to develop mental health promoting culture into school context, thus accomplishing the idea "to consider schools as part of a wider network involved in guaranteeing mental health in children and adolescents in local communities" (51).

The second aim of the study is to achieve a better understanding of ED. This is particularly relevant since ED is a complex construct including emotional, cognitive and behavioural components. The most common method to measure ED is based on self-report questionnaires, mainly the DERS (4). In the present study, we will include a comprehensive assessment that will evaluate both the use of emotional regulation skills and the frequency of dysfunctional behaviours as potential proxy variables of ED. Moreover, the questionnaires focusing on depression, anxiety, family functioning, school climate, and stressful events will allow to evaluate the influence of clinical and social factors as potential determinants of ED.

According to the bio-social model (53), ED implies the presence of a biological vulnerability which refers to a specific pattern of emotional processes characterized by high reactivity to external stimuli, high intensity of experienced emotions, and slow return to baseline (53). This pattern is directly associated with the expression of emotions – the overt behaviors. Indeed, the complex phenomenon of emotions has neural substrates in bottom-up subcortical brain regions, while emotion regulation is mainly assured by top-down cortical brain networks (21, 31). It has been argued that, when high-emotional reactivity is coupled with impairment in top-down control pathways, psychopathology is likely to occur (31). Among the neurobiological processes underlying such regulation, stress has been suggested to play a key role considering also its ability in directly influencing cerebral circuits implicated in emotions processing (24). Salivary cortisol is the most widely used methods to assess HPA axis (dys)functioning. However, cortisol represents only one of the products of HPA axis activation. In the present study, we will assess both cortisol and other inflammation mediators such as the cytokine levels. This will contribute to overcome one of the limits of available studies as they mostly focused only on cortisol level. Moreover, it will be possible to better understand the mechanisms through which ED operate (30). Given the paucity of studies in adolescents, data from the present trial could be particularly informative as they will make possible to accumulate knowledge about the relation between HPA axis profile in a general population samples of adolescents.

Trial Status

The protocol has been registered at ClinicalTrials.gov with the identifier number of NCT04349709. The recruitment started in November 2019 and it will be approximately completed by November 2022.

Abbreviations

ED: emotional dysregulation; SEL: Socio-Emotional Learning; HPA: hypothalamic-pituitary-adrenal axis; DBT: Dialectical Behavioural Therapy; DBT STEPS-A: Skills Training for Emotional Problem Solving for Adolescents.

Declarations

Authors' contributions {31b}

LP is the principal investigator, and she conceived the study with LRM, ML, RR, AC. AC and NL participated in the development of the protocol by providing their expertise about biological and molecular mechanisms. CF and AM will provide their statistical expertise in the clinical trial design. LP, SM will assure data collection and data entry and they coordinated and provided the intervention. VZ and AC will guarantee proper biological samples collections, the measurements of the biological variables and bioinformatic analyses. All authors have contributed to the refinement of the study protocol and have approve the final manuscript.

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Availability of data and materials {29}

Reported in {31c}.

Ethics approval and consent to participate {24}

The trial had been approved by the Comitato Etico IRCCS Fatebenefratelli (approval 40/2019). A translated copy of the document is reported as additional materials.

Competing interests {28}

The authors declare that they have no competing interests.

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