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Novel rapid treatment options for adolescent depression

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ABSTRACT

There is an urgent need for novel fast-acting antidepressants for adolescent treatment-resistant depression and/or suicidal risk, since the selective serotonin reuptake inhibitors that are clinically approved for that age (i.e., fluoxetine or escitalopram) take weeks to work. In this context, one of the main research lines of our group is to characterize at the preclinical level novel approaches for rapid-acting antidepressants for adolescence. The present review summarizes the potential use in adolescence of non-pharmacological options, such as neuromodulators (electroconvulsive therapy and other innovative types of brain stimulation), as well as pharmacological options, including consciousness-altering drugs (mainly ketamine but also classical psychedelics) and cannabinoids (i.e., cannabidiol), with promising fast-acting responses. Following a brief analytical explanation of adolescent depression, we present a general introduction for each therapeutical approach together with the clinical evidence supporting its potential beneficial use in adolescence (mainly extrapolated from prior successful examples for adults), to then report recent and/or ongoing preclinical studies that will aid in improving the inclusion of these therapies in the clinic, by considering potential sex-, age-, and dose-related differences, and/or other factors that might affect efficacy or long-term safety. Finally, we conclude the review by providing future avenues to maximize treatment response, including the need for more clinical studies and the importance of designing and/or testing novel treatment options that are safe and fast-acting for adolescent depression.

1. Introduction

Adolescence is a period of significant development that begins with the onset of puberty and transitions between childhood and adulthood. It is divided in three stages, which include early (10 to 13 years), middle (14 to 17 years), and late adolescence/young adulthood (18 to 21 years and beyond) [1,2]. This life period is characterized by rapid physical, psychological, and social age-related changes, making it a particularly vulnerable period for the development of psychopathology [3]. In this context, major depression disorder, which is a leading global cause of disability [4,5] and global burden [6], habitually onsets in adolescence, affecting around 2–8% of young individuals (10–19 years old [7,8]). It shows clear underlying sex differences in relation to puberty [9,10], with similar rates typically found during early adolescence [11–13], and noticeable differences emerging at later ages, when females showed an augmented propensity to depression [14–16]. However, in the adolescent populations this propensity has been consistently rising over the past years across many countries, especially for females, as compared to later adult periods in which the sex-gap seemed to have narrowed [17] (reviewed by [18]). Several causal factors might be worsening the mental health of adolescents in general, but more particular in female adolescents, such as cyber-bullying, education-related pressures, an earlier emergence of puberty, as well as other novel risk factors (i.e., social media use, impact of COVID pandemic, comorbid eating disorders, etc.) [18]. Moreover, this higher risk of experiencing depression in adolescents parallels an increase trend in suicidal behavior, a leading cause of death among adolescents worldwide, and in non-fatal suicidal behaviors (suicidal ideation and intentional self-harm), a significant cause of morbidity and the strongest predictors of suicide (see further details as reviewed by [18]).

Given the increasing trends over the past two decades in many countries in depression and suicide rates in adolescence (e.g., [6,18]), there is an urgent need to direct more resources to screening and prevention programs, as well as to develop novel safe and fast-acting

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therapeutical options; this is especially relevant given the scarce pharmacological options available for this age group and the fact that classical antidepressants require repeated administrations during many days or weeks to work. In particular, the initial treatment for adolescent depression involves psychotherapy, pharmacotherapy for moderate to severe cases, although only two drugs are approved by the U.S. Food and Drug Administration (FDA) (selective serotonin reuptake inhibitors: fluoxetine, age 8 and above, or escitalopram, age 12 and above), or a combination of both (recently reviewed by [19]). This absence of pharmacological options during adolescence is caused, in part by the fact that symptom criteria, as defined in the diagnostic and statistical manual of mental disorders (DSM), are not adapted for age and biological sex, and there are differential underlying mechanisms behind the disorder as compared to adulthood (e.g., [13,20]), which leads to low diagnostic validity for adolescent major depression disorder, as symptoms change across the lifespan [21,22]. In particular, prior findings suggest that adolescent major depression disorder is characterized by significant aberrant functional connectivity between several brain regions involved in emotion processing and regulation (e.g., amygdala hyperactivity and anterior cingulate cortex; reviewed by [22]) during a period in which these regions are still undergoing development [23]. Thus, these maturation processes that occur in brain regions and systems that play a major role in the neuroanatomical and neurobiological substrate of depression together with the contextual factors such as early life adversity and stress factors (as previously described) might be in part responsible for the first-line prolonged drug treatments to either fail to respond or show lower efficacy [24–27], and/or to induce more side effects than expected and even harmful responses (i.e., increased suicide ideation; [28]). In fact, evidence-based treatments fail to improve symptoms in approximately 30–40% of adolescents [27–32] (reviewed by [19]), leaving a big percentage of adolescents with treatment-resistant depression and therefore with a higher risk for suicide.

On top of that, there are clear sex differences in treatment response for certain antidepressants (see [33–35]), with females typically being less responsive and/or experiencing more side effects than males, although the direction of the sex-change is not always that clear (reviewed by [36]). Moreover, preclinical studies in adolescent female rodents are scarce in the literature [37], and sex bias still persists in clinical trials within certain medical fields, with potential later negative consequences for the health of all individuals [38]. Therefore, while characterizing additional treatments to provide a rapid relief of depressive symptoms during adolescence, optimal designs should evaluate potential sex differences by including sex as a biological variable in all preclinical studies, and by incorporating enough females in the clinical studies, to later ensure an optimal treatment outcome (for recent comments about this topic, see [35,39]). The end goal will be to provide novel rapid treatment options, potentially based on different mechanisms of action [40], to prevent the wait for efficacy during adolescence and improve both treatment response and/or suicidal behaviors.

Against this background, the present review presents potential novel rapid antidepressants treatments, such as neuromodulators (i.e., mainly electroconvulsive seizures, but also other approaches), as well as emerging pharmacological agents (i.e., ketamine and classical psychedelics, cannabidiol and other cannabinoids) for adolescent depression (see Fig. 1). Although some of these approaches are already in use for

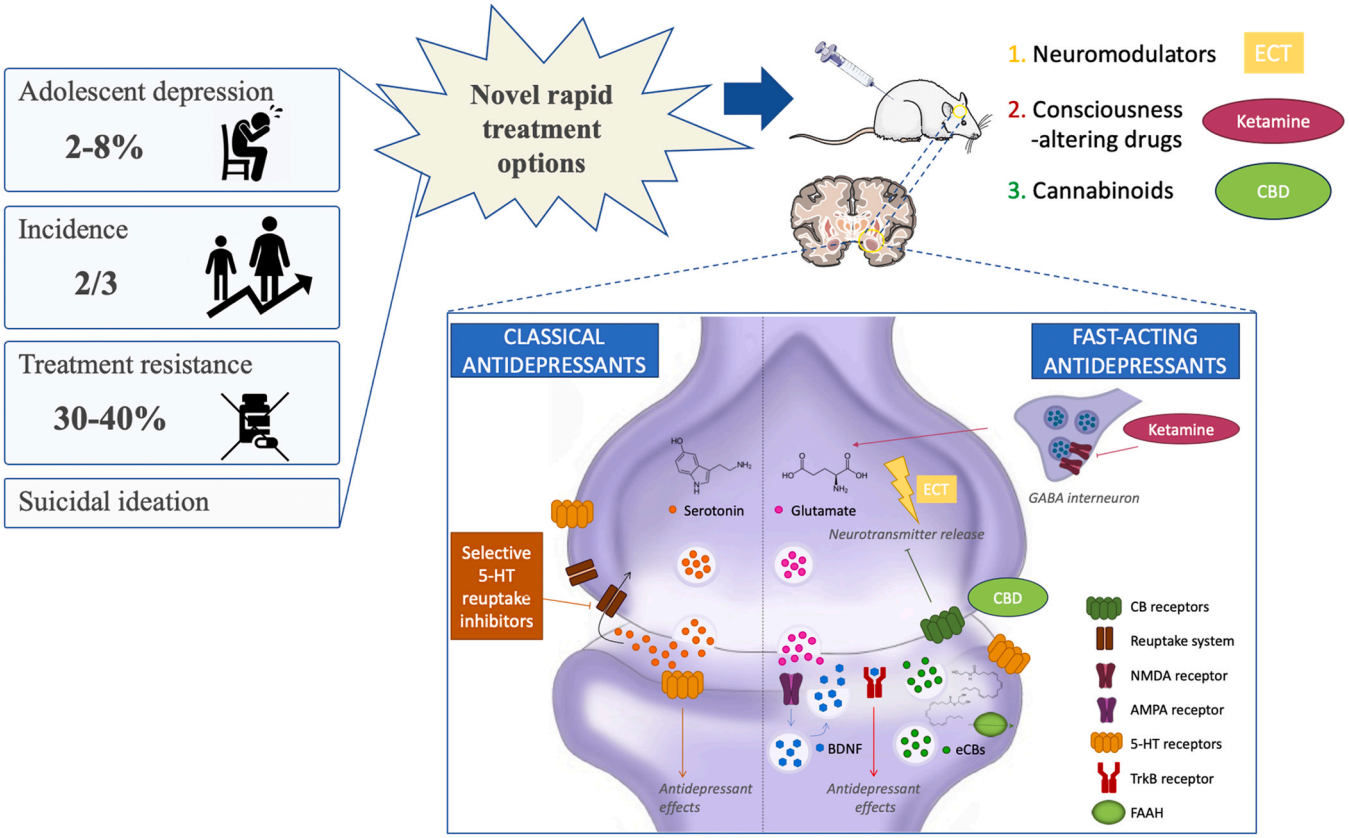

Fig. 1. Novel rapid treatment options for adolescent depression. Schematic representation of the rates of adolescent depression, incidence, treatment resistance, and suicidal ideation, as well as of the mechanisms of action of the classical antidepressants utilized nowadays at the clinical level (i.e., selective 5-HT reuptake inhibitors: fluoxetine, escitalopram), as compared to novel rapid treatment options (1) Neuromodulators: ECT; (2) Consciousness-altering drugs: ketamine; (3) Cannabinoids: cannabidiol). Abbreviations - - AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF: brain-derived neurotrophic factor; CB: cannabinoids; CBD: cannabidiol; ECT: electroconvulsive therapy; eCBs: endocannabinoids; FAAH: Fatty acid amide hydrolase; 5-HT: 5-hydroxytryptamine or serotonin; NMDA: N-methyl-D-aspartate; TrkB: Tropomyosin receptor kinase B.

adult patients, they still require additional studies to ensure efficacy and safety in adolescence. Following a general introduction, we will first describe the clinical evidence already supporting the potential beneficial use of each approach in adolescence (mainly extrapolated from prior successful examples for adults), to then report recent and/or ongoing preclinical studies, which will include results from our research group further evaluating each approach (i.e., potential sex- and age-differences, long-term safety, etc.). In this context, it is worth mentioning that adolescence appears to be a highly conserved developmental stage across species in terms of neurobehavioral and physiological characteristics, and thus, these similarities provide both face and construct validity for the use of rodent models as tools for the study of adolescence [41]. Similar to the stages observed in humans, and based on the onset of puberty, periadolescence in rodents could be divided into early (postnatal day, PND 21–34), mid (PND 34–46) and late adolescence (PND 46–59) [42], providing particular windows of vulnerability to psychopathology and therapeutic strategy [43]. As mentioned earlier, a special relevance will be given to evaluating potential differences induced by sex as a biological variable [10,37,44–45], since females have been traditionally excluded and/or underrepresented both in preclinical and clinical studies, while are currently showing the highest increases in adolescent depression rates (reviewed by [18]). Finally, we will conclude the review by providing some general lessons learnt from the literature and what could be done in the future to design novel treatment options for adolescent depression.

2. Neuromodulators: electroconvulsive seizures and other neuromodulators

Neuromodulation approaches are non-pharmacological treatments based on the alteration of neural circuitries through stimulation delivered either in an invasive or non-invasive manner [46]. They have emerged as alternative and promising clinical options for various psychiatric disorders, including major depression disorders (reviewed by [47]). In particular, different neurostimulation techniques are really promising in terms of achieving rapid (within days) or ultra-rapid (minutes to hours) psychotherapeutic improvements in patients with treatment-resistant depression (i.e., electroconvulsive therapy: [48]; deep-brain stimulation: [49,50]), therefore presenting themselves as great alternatives to be used for adolescent depressed patients.

2.1. Electroconvulsive seizures

The first neuromodulation approach, and most studied up until today, is electroconvulsive therapy, a procedure that applies electrical stimulation to produce a generalized seizure. It was introduced, almost a century ago [51] and is still used in psychiatry as a non-pharmacological antidepressant treatment that offers a safe, rapid and long-lasting therapeutic response in adults for a variety of mental disorders when they do not respond to pharmacological treatment and/or psychotherapy [52–54]. Particularly, clinical studies have consistently showed that electroconvulsive therapy improves a wide range of symptoms in adult patients with treatment-resistant depression, with an average beneficial response rate of 60 to 80% [55,56]. Recent meta-analyses have validated the efficacy of electroconvulsive therapy for managing depressive patients (e.g., [57]) and for preventing relapse and recurrence of depression in adults with major depressive disorder (e.g., [58]). Lately, efforts are directed to facilitate clinician decision making by standardizing a protocol (e.g., [59]) in terms of the type of stimulus applied, the regions stimulated, and the stimulus parameters utilized (i.e., stimulus duration and/or pulse width), as well as in the anesthetic used (e.g., [60]). Homogenizing the protocol applied during electroconvulsive therapy will help improve treatment efficacy and acceptability, while minimizing the emergence of the most common side effects (i.e., cognitive impairments; see for example [61]).

2.1.1. Clinical evidence supporting its use in adolescence

Despite the strong evidence supporting the efficacy of electroconvulsive therapy in adults, its use in adolescents is much less common, probably due to an inadequate knowledge or lack of clinicians' experience, paired with the sparse literature available covering this age group (e.g., [62,63] and reviewed by [64]). Particularly, a recent study concluded that only 1% of psychiatrists had an advanced knowledge on electroconvulsive therapy, while two-thirds rated their knowledge from none to negligible (e.g., [63]). This lack of expertise conditioned the attitude towards its use, since child and adolescent psychiatrist with some or advanced knowledge and experience were more likely to believe that electroconvulsive therapy was a safe and effective treatment across all age groups [62,63]. Additionally, the absence of large-scale studies and legal restrictions regarding young patients, together with an inadequate data about its potential side effects, could also be responsible for the infrequent use of this therapy in adolescents [65–67]. However, since the American Academy of Child and Adolescent Psychiatry (AACAP) published a practice parameter for treating children and adolescents with electroconvulsive therapy, there has been a promising significant growth in the number of publications focused on its acute and repeated use for adolescents with treatment-resistant depression and suicidal symptoms, as well as other neuropsychiatric disorders like catatonia and schizophrenia (e.g., [55,64,67–73]).

Interestingly, when comparing the treatment outcome for adulthood vs. adolescence, electroconvulsive therapy seemed to induce a similar response rate, as well as tolerability and cognitive side-effects, for patients with mood and psychiatric disorders (e.g., reviewed by [64]). The overall response rates to electroconvulsive therapy in children and adolescents with depression ranged between 51% and 92% depending on the study and the type of disorder [74–76,67,64] (see also Table 1 for more details). For example, and similarly to adults, adolescents diagnosed with a psychotic subtype of depression showed a better response to electroconvulsive therapy (85% improvement as compared to 63% in patients without a psychotic subtype) (reviewed by [77]). Furthermore, electroconvulsive therapy decreased depressive and suicidal symptoms during adolescence by 49% in patients with suicidal ideation, and by 54% in patients with a suicide attempt [71]. A similar study reported that electroconvulsive therapy in a sample of adolescents with severe mood disorders decreased suicidal behavior, reduced depressive symptoms, and improved overall functioning, while suggested the need for prospective studies using larger samples in order to determine its effectiveness and safety in refractory mood disorders in adolescents [78]. Also, while electroconvulsive therapy was effective and safe for improving suicidal ideation and depressive symptoms of adolescent patients with major depressive disorder, the partially impaired cognitive function recovered gradually over time (i.e., effects evaluated up to 6 weeks after treatment) [79]. In terms of tolerability, electroconvulsive therapy was generally well tolerated in adolescents, and was rarely discontinued due to side effects, being the most common outcomes headache, nausea, vomiting, confusion, and muscle soreness (reviewed by [64]). As mentioned earlier, the cognitive side effects evoked during the first few days after treatment appeared to be transients in adolescents, as observed for adult patients [63,80,81]. Similarly, a recent study also reported that antidepressants combined with electroconvulsive seizures were associated with high response rate and safety for treating depression regardless of age, with similar side effects in adolescence and adulthood, but with a stronger expression of suicide ideation in depressed adolescents [82]. However, and on a different note, this later study was recently criticized in a correspondence article in Journal of Affective Disorders [83], in which, based on some flaws presented in the discussed study and others, a high rate of cognitive impairment and brain damage from electroconvulsive therapy with adolescents is suggested. Based on this comment future studies should be better design, for example, by including a proper placebo-control group, by stating how memory impairment is measured, as well as by evaluating the progression of this impairment to assess whether is transient and/or permanent

Table 1
Clinical and preclinical evidences supporting the use of electroconvulsive seizures in adolescence.

Reference	Clinical subjects	Treatment	Outcome	Side effects
[67]	Sixty-two adolescents (14-18 years old) with MDD, bipolar disorder, schizophrenia or schizoaffective disorde	Bilateral-bitemporal led placement; brief pulse of ECT administered 3 times per week for up to 7 to 12 sessions (depending on their clinical response); anesthesia with propofol (1 mg/kg); muscle relaxation with succinylcholine (0.5 mg/kg)	Improvement of manic, depressive, psychotic, and catatonic symptoms	Memory complaints, headache, prolonged seizure, nausea/vomiting, and manic episode
[71]	Two hundred and seventy-eight adolescents (12-17 years old) with MDD and suicidal symptoms	Bitemporal led placement; brief pulse of ECT administered 3 times in the first week, then 2-3 times for up to 6-12 sessions; anesthesia with propofol (1.5-2 mg/kg); muscle relaxation with succinylcholine (0.5-1 mg/kg)	Improvement of depressive symptoms and decreased suicidal ideation	Subjective memory complaints, headache, body pain, delirium, nausea/vomiting
[74]	Twenty-five adolescents (13-18 years old) with MDD, schizophrenia, psychosis NOS, acute and transient psychosis, schizoaffective disorder, OCD, catatonia	Bilateral led placement; brief modified pulse administered 3 times a week for up to 6- 12 sessions; anesthesia with sodium thiopental (150-450 mg); muscle relaxation with succinylcholine (30-60 mg)	Improvement of depressive, psychotic, and catatonic symptoms	Post-ECT confusion, prolonged seizures, headache, nausea/vomiting and manic episode
[75]	Thirteen adolescents (15-18 years old) with MD	Right unilateral or bitemporal led placement; Ultra-brief or brief pulse administered 2-3 times a week for up to 6-22 session; anesthesia with propofol, remi-fentanyl and/or ketamine; muscle relaxation with succinylcholine	Improvement of depressive symptoms	Transient subjective cognitive impairment, prolonged seizure, headache, muscular pain, nausea/ vomiting
[76]	One hundred and seven adolescents (10-18 years old) with MDD, bipolar disorder, depression secondary to Tay-Sachs disease or psychosis	Bifrontal, bitemporal or unilateral lead placement for a mean of 10.5 sessions	Improvement of depressive and mania symptoms	Cognitive impairment, tardive seizure, headache, muscle soreness, nausea/ vomitin
[78]	Fifty-four young subjects (no range of age provided) with unipolar depression, bipolar depression or mood disorder NOS	Bilateral, unilateral or mix lead placement administered 3 times a week, with a mean of 13.7 session; anesthesia with methohexital sodium (1 mg/kg); muscle relaxation with succinylcholine (0.8 mg/kg)	Overall improvement	Memory loss, confusion, prolonged seizures, headache, fatigue
[79]	One hundred and sixty adolescents (13-18 years old) with MDD and suicidal ideation	ECT combined with classical antidepressants (selective serotonin reuptake inhibitors); bilateral temporal led placement; pulse 1.0 ms; ECT administered during 2 weeks with 8 rounds; anesthesia with propofol (1 mg/kg); muscle relaxation with succinylcholine (0.5 mg/kg)	Improvement of depressive symptoms and suicide scores	Transient cognitive impairment as compared with control group, headache, discomfort and jaw tension
[80]	Ten young subjects (no range of age provided) with bipolar disorders or MDD	Led placement not provided; pulse and sessions per week not provided; mean of 9.8 ECT sessions; anesthesia and muscle relaxation details not provided	Overall improvement	Subjective memory impairment immediately after ECT course
[81]	Sixteen adolescents (13-18 years old) with unipolar and bipolar depression	Bilateral, right unilateral or mix led placement; ECT administered 3 times a week, with a mean of 10.8 sessions; anesthesia with methohexital sodium; muscle relaxation with succinylcholine	Overall improvement	Impairments in verbal memory, digit span, and verbal fluency 7-10 days after ECT (back to normal at 8.5 months); motor strength and executive processing not affected
[82]	One hundred and ten adolescents (13-18 years old) and adults (19-65 years) with depression or bipolar disorder	Antidepressants and ECT; bitemporal led placement; pulse not provided; ECT administered 3 times a week, every other day until patient achieved remission or refuse therapy; anesthesia with atropine (0.5 mg) and etomidate fat emulsion (0.3 mg/kg); muscle relaxation with succinylcholine (1-1.5 mg/kg)	Improvement of depressive symptoms and suicidal scores	Transient memory impairment, headache, nausea/vomiting and muscle soreness
[91]	One thousand and sixty-six patients divided into 4 age groups (15 to 39, 40 to 60, 61 to 80, and 81 to 99 years old), based on age at the time of treatment, with depressive episode or recurrent MDD	Unilateral, bifrontal, bitemporal led placement; pulse 0.05 ms, greater than 0.5 ms or less than 0.5 ms; sessions per week not provided; mean of 7.8 ECT sessions; anesthesia and muscle relaxation not provided	Improvement in health-related quality of life in male and female patients with depression in all age groups	Not reported
[25]	Male and female Sprague-Dawley adolescent (PND 46-50) and adult (PND 73-77) rats (naïve vs. MD).	ECS sessions (95 mA, 0.6 s, 100 Hz, 5 sessions, 1 session/day)	Efficacious in males, but not in females	Not evaluated
[96]	Female Sprague-Dawley adolescent (PND 46-50) and adult (PND 95-99) rats	ECS sessions (55, 75 or 95 mA, 0.6 s, 100 Hz, 5 sessions, 1 session/day)	Lowest tested intensities (55-75 mA): efficacious in adult females; no effects in adolescence	Not evaluated
[97]	Male and female Sprague-Dawley adolescent (PND 44-51) rats	LTZ pre-treatment (1 mg/kg, i.p., 8 days) followed 3 h later by a daily ECS sessions (95 mA, 0.6 s, 100 Hz, 5 sessions, 1 session/ day)	Efficacious in males, but not in females; ECS+LTZ: antidepressant response in females	No long-term cognitive or affective side effects; certain long-term benefits in male rats (shorter times when resolving a maze)

Abbreviations: ECS: electroconvulsive seizures; ECT: electroconvulsive therapy; LTZ: letrozole; MD: early-life maternal deprivation; MDD; major depressive disorder; NOS; not-otherwise specified; OCD: obsessive-compulsive disorder; PND: post-natal day.

[83], since there is a lack of studies evaluating the potential long-term consequences of the adolescent treatment that might be projecting into adulthood. Finally, the mortality rate and/or potential anesthetic-related complications in adolescents appeared to be similar, or possibly lower than adults treated with electroconvulsive therapy (see the systematic review and pooled analysis by [84]). Nevertheless, some unique factors should be considered for pediatric electroconvulsive therapy, like the potential need for a preoperative anxiolytic and/or an inhalational induction of anesthesia, which might be unfavorable for evoking the required seizure needed for a successful treatment (e.g., [85, 86]).

Overall, the efficacy, safety, and applicability of current electroconvulsive therapy practices in adolescents are the result of several advances in treatment delivery, which have focused on improving efficacy (i.e., adjusting the electrical dose, stimulus parameters and/or electrode placement), and reducing the potential cognitive side effects, such as anterograde and retrograde memory [59,87]. In general, recent reports suggest that electroconvulsive therapy is a safe and effective treatment in children and adolescents with mood disorders and should be considered in severe and treatment refractory cases. In fact, a recent analysis on the use of electroconvulsive therapy in children and adolescents in Europe, which also included expert information and future guideline recommendations, concluded the need for novel high-quality evidence, improved knowledge and additional training of child and adolescent psychiatrists to increase its clinical use, since its nowadays use seems merely reserved for accidental circumstances [73]. Moreover, age and sex are important factors to be consider when electroconvulsive therapy is used [88–92], as previous studies have shown that women appeared to require less charge to induce an optimal seizure than men at the same age, and for both sexes the charge needed increased with age [93].

2.1.2. Further preclinical characterization in adolescence

Electroconvulsive therapy is modeled in rodents through the induction of electroconvulsive seizures [94] and can be used in pre-clinical research to characterize the optimal conditions needed to exert the most beneficial treatment outcome in terms of its antidepressant-like effects vs. its potential cognitive side effects, while including sex as a biological variable. In this context, our research group has been relying on this procedure to describe the antidepressant-like effects of electroconvulsive seizures, first exclusively in adult male rats [95], to then include changes in efficacy by age (adolescence vs. adulthood), sex and/or early-life stress exposure [25]. Moreover, we have evaluated potential changes in efficacy due to different dose-intensities used to induce seizures during adolescence and adulthood [96], as well as the potential role of inhibiting the biosynthesis of estrogens during adolescence in the antidepressant-like response observed [97]. Finally, we have also assessed potential long-term effects emerging in adulthood following adolescent treatment, such as the hypothetical variations in cognitive performance [97]. Table 1 includes a summary of the data available in adolescent rats.

Besides our recent studies, prior findings evaluating the antidepressant-like effects of electroconvulsive seizures were almost exclusively done in adult male rodents [98–100,94,101], with little to inexistent data for adolescence and females. In this context, and in an attempt to advance the field forward, we proved age- and sex-specific differences in the antidepressant-like potential of repeated electroconvulsive seizures (95 mA for 0.6 s at a frequency of 100 Hz square wave pulses, pulse width 0.6 ms, 1 shock/day, 5 days), both in naïve and maternally deprived (a model of early-life stress) Sprague-Dawley rats [25]. Particularly, repeated electroconvulsive seizures exerted similar antidepressant-like effects in male adolescent [25,97] and adult [25,95] rats, although with a shorter response in adolescence, since efficacy was observed 1-day post-treatment in adolescence as compared to up to 3 days post-treatment for adulthood. Contrarily, the same procedure rendered ineffective and/or even deleterious in female adolescent and adult rats [25,96,97].

Based on clinical data reporting that females require a lower electrical charge to induce an effective convulsion when applying electroconvulsive therapy [93], we performed an experiment evaluating the response elicited by different dose intensities (55, 75 and 95 mA; 0.6 s, frequency of 100 Hz square wave pulses, pulse width 0.6 ms, 1 shock/day, 5 days) exclusively in female rats (both adolescents and adults) [96]. Interestingly, when the intensity of the pulse applied during electroconvulsive seizures was lowered from 95 mA to 75 or 55 mA, an antidepressant-like effect was observed in adult female rats, while still no beneficial response was detected for adolescent female rats [96]. These results suggested a decreased sensitivity to the antidepressant-like response induced by electroconvulsive seizures during adolescence for this particular sex as compared to adulthood. These disparities in efficacy paralleled some changes in the features of the convulsions elicited by the treatment. Particularly, adult female rats displayed longer tonic phases, paired with shorter clonic ones, and a much quicker recovery time (almost two-fold), as compared to adolescent female rats, in line with the data suggesting that changes in seizure duration could be considered as a potential marker of efficacy [102], and proposing a possible mediator of the differential behavioral response observed with age [96].

Up to this point our data suggested that electroconvulsive seizures was less efficacious in adolescent female rats. Given the role of sex steroids as important modulators in the efficacy of certain antidepressants (e.g., [103–106]), we evaluated how estrogens might alter the antidepressant-like response of electroconvulsive seizures in adolescent male and female rats. To do so, we utilized letrozole, an inhibitor of the aromatase that converts androgens into estrogens [107], and that has been previously used in the context of other sex-related antidepressant-like responses (see [108] for fluoxetine; and [109] for our own studies with ketamine). As previously reported [25,96], while repeated electroconvulsive seizures (95 mA) induced an antidepressant-like response exclusively in adolescent male rats, its combination with letrozole rendered efficacious in female adolescent rats [86], demonstrating that the production of estrogens was responsible for the lack of effects observed in females. These preliminary results proposed a role for the biosynthesis of estrogens and/or for the accumulation of testosterone in the therapeutical response induced by electroconvulsive seizures in adolescent rats [97].

Moreover, when characterizing the effects of electroconvulsive seizures in adolescence one should consider the potential long-term consequences emerging later on due to this early intervention, in terms of future long-term changes in cognitive performance in adulthood (e.g., [110–112,100]). On the contrary, our preclinical data is rather promising in terms of actually showing certain long-term benefits, although exclusively for male rats. Particularly, we recently demonstrated that the induction of electroconvulsive seizures in adolescence improved cognitive performance in adulthood, and although these effects were exclusively observed in male rats, they suggested a better spatial learning and memory performance [97]. Unfortunately, no long-term benefits were observed for female rats at one of the doses tested (95 mA), probably due to the lack of efficacy during adolescence [25, 97]. These preclinical results are really promising in terms of proving long-term treatment safety, particularly given the clinical concern on how electroconvulsive seizures during adolescence might disrupt normal brain development of key limbic networks undergoing crucial phases of their development and affect cognitive function permanently, since prior studies were mainly centered in short-term side effects [63, 80–83], but persistent evaluations are rare and/or missing. Moreover, and to add to the ongoing debate regarding whether the cognitive effects observed following electroconvulsive therapy might be linked to the anesthetic used to apply the treatment, it is worth noting that in all of our procedures in rats, electroconvulsive seizures were induced in the absence of anesthesia. Therefore, our experimental model contributes to discriminate the effects induced by electroconvulsive seizures vs. the

ones from the anesthesia. Consequently, this moves away from the conditions utilized for electroconvulsive therapy in humans, in which anesthesia might be interfering with the observed antidepressant-like effects and/or affecting the emergence of side effects (i.e., changes in cognitive performance).

In conclusion, based on our studies and on the literature supporting its clinical safety in adolescence, electroconvulsive seizures should be encouraged to be used in cases of treatment-resistant depression during adolescence, while adjusting the parameters used for seizure induction to favor efficacy over side effects and adhering to sex-specific considerations [113].

2.2. Other neuromodulators

Besides electroconvulsive therapy, other neuromodulators could be potentially used for adolescent depression, however, the data supporting its use is either completely underexplored, or still at the initial stages for adult patients. One of the early brain stimulation techniques that emerged in 1960 s is deep brain stimulation, an invasive procedure where a lead is placed at certain specific brain areas and connected to an extracranially implanted pulse generator [114]. Although, the FDA approved deep brain stimulation in 2001 to treat tremors in Parkinson's Disease adult patients [115], its efficacy in treatment-resistant major depression, while with promising rapid responses, is still under evaluation [49,50,116,117]. In recent clinical trials, deep brain stimulation seemed to be effective in reducing depressive symptoms in adults, but with a moderate effect size and a very low certainty of evidence (e.g., [118]). Moreover, evidences about its long-term efficacy in depression are insufficient since studies have been mostly designed as cross-over trials and with few adult participants [119]. In terms of adolescent patients, there are yet no clinical evidences of its beneficial use.

Recently, novel non-invasive brain stimulation techniques have emerged as alternatives to invasive modalities given the ease of application, safety, tolerability, and reversibility (e.g., [120]). One of the most well-studied forms is repetitive transcranial magnetic stimulation, which was approved by the FDA in 2008 to treat major depression disorder in adults by applying pulsed magnetic fields to induce an electric current in a localized region of the cerebral cortex [121,122]. Although repetitive transcranial magnetic stimulation is well-tolerated and is relatively safe for treating depression, with minimal mostly mild and transient side effects in the adult population, not much knowledge is available regarding its use in adolescence [123]. However, of the 10 publications or so describing this treatment for 112 unique adolescent participants with depression, the results are quite promising (reviewed by [124]). For example, repetitive transcranial magnetic stimulation in adolescents showed similar clinical effects, safety, and tolerability as the ones described in adults [124]. In fact, preliminary evidence suggested that this approach proved signs of long-term safety since it did not associate with long-term deterioration in symptoms of depression or cognitive functioning, and on the contrary, it even seemed to induce some long-term benefits in some subjects [125]. Moreover, a larger international study should be soon providing more data about the safety and effectiveness of this therapy in depressed adolescent patients (see https://classic.clinicaltrials.gov/ct2/show/NCT02586688). Other forms of non-invasive neuromodulation (e.g., transcranial direct current stimulation and vagus nerve stimulation) are also available, although their treatment safety and efficacy are still being investigated in clinical trials with adult patients [46], and the knowledge for children and adolescents is limited to a few small randomized controlled trials and pilot studies (see review [114]).

In conjunction, while certain progress has been made for various neuromodulation interventions, their approval as potential adolescent treatments still remain limited, especially since optimal stimulation parameters still lack agreement. Future studies should center in standardizing the protocols for these non-pharmacological techniques so they could be safely applied as adjuvant treatments for adolescent depression. Overall, and as of today, from all of the neuromodulators just described, the general consensus should be to further encourage the use of electroconvulsive therapy in cases of adolescent treatment-resistant depression in which fast-acting responses are needed.

3. Consciousness-altering drugs: ketamine and classical psychedelics

Since the FDA approved in 2019 esketamine (Spravato) as a rapid-acting antidepressant for treatment-resistant depression, other N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., [126,127]), as well as many consciousness- and/or experience-altering psychedelics drugs (i.e., psilocybin, lysergic acid (LSD), diethylamide methylenedioxymethamphatemine (MDMA), mescaline, etc.) have been under characterization at low doses for several psychiatric conditions (see many recent reviews covering this hot topic [128–131]). Since most of the clinical data available in this regard is centered in adult patients, a better understanding of the effects induced by these drugs in adolescence, including their long-term safety would provide psychiatrists with the confidence necessary to use these novel fast-acting options for this age group.

3.1. Ketamine

Ketamine was synthesized in the 1960 s while searching for novel anesthetic drugs similar to phencyclidine, but with shorter action times and reduced adverse effects (reviewed by [128,132,133]). While the anesthetic clinical use of ketamine was approved by the FDA in 1970, its application for psychiatric disorders began with the discovery of the relationship between NMDA glutamate receptors and synaptic plasticity, memory and learning processes [134], and in the context of the psychedelic-like effects of the drug [135]. Moreover, the chronic administration of NMDA receptor antagonists induced the same behavioral and neurochemical effects as certain classical antidepressants [136]. In this context, ketamine was characterized as an NMDA receptor antagonist [137] and was applied in combination with psychological therapy in the treatment of major depression, anxiety and other stress-related disorders (for further information see [138]). In the year 2000, the first randomized placebo-controlled double-blinded trial was done in 7 adult patients that received a sub-anesthetic dose of ketamine (0.5 mg/kg) intravenously [139]. Ketamine showed significant improvements in depressive symptoms within 72 h after treatment [139]. From this introductory clinical study, up until the day the FDA approved ketamine (S enantiomer) for treatment-resistant depression and suicidal ideation in adults, many other clinical studies have centered in validating its efficacy and long-term safety (for a more detail history of events see [128]), as well as the potential ethical considerations surrounding these types of treatments [140]. In particular, one of the main negative aspects that require some caution for its therapeutic use is related to the association of subanesthetic doses of ketamine with psychiatric symptoms resembling psychosis and schizophrenia [141], and as described in a recent randomized controlled trial in adult healthy volunteers [142]. In this context, some studies have suggested the therapeutic vs. detrimental effects of NMDAR blockade by ketamine might be circuit dependent [143], such as that the very rapid, antidepressant effects of intranasal ketamine may involve an acute modulation of reward circuits and sub-acute increase in neuroplasticity [144], while its detrimental effects (i.e., dissociative and psychedelic properties) might be driven by dose- and context-dependent disruption of large-scale functional networks [16R1] Overall, and balancing all prior data on ketamine's effects (recently reviewed by [128–130]), the European Commission also followed with the approval of esketamine as a short-term treatment for adults presenting a moderate to severe episode of major depressive disorder [146]. The recommendation is that ketamine should be given alongside an oral antidepressant in situations considered a psychiatric emergency, and with the objective of rapidly

reducing depressive symptoms [146]. Current research is monitoring and still learning about the effects of ketamine in terms of standardizing the dosage needed and the frequency of administration for efficacy duration, and other pharmacological events that could be adjusted to improve the therapeutical response and avoid potential side effects, including increasing the scarce available knowledge on the potential long-term impact of its repeated treatment (e.g., safety and tolerability; [147]) such as its abuse potential [148]). Overall, ketamine is a promising fast-acting candidate antidepressant to be fully characterized for adolescent depression.

3.1.1. Clinical evidence for its use in adolescence

Despite the good therapeutical response induced by ketamine in adults, its use in adolescence is still understudied [149]. This might be mainly due to concerns on safety on the developing brain which limits its research in this young population. Particularly because ketamine, as mentioned earlier, at subanesthetic doses is also psychotogenic (i.e., its repeated administration is an established preclinical model of schizophrenia; [150]), and although this model is normally observed at higher dose-ranges than the ones used to induce an antidepressant-like effect (e.g., [143,144]), and these effects seemed to be mediated by different mechanisms (e.g., [143,145]), since adolescence is a period of great plasticity during neurodevelopment [23], the potential use of ketamine as a major therapeutic option for adolescent people with depression should be further evaluated. However, there is plenty of prior data reporting that ketamine is well tolerated and safe for use in children and adolescents when administered as an anesthetic, analgesic and sedative agent. In this context, a recent systematic review that evaluated the safety of repeat dosing of ketamine in children and adolescents concluded that the use of ketamine is well tolerated and safe in this age group, even when given repeatedly in regimens similar to those used for the treatment of depression in adults [151]. Similarly, ketamine was associated with comparable clinical benefits, safety and tolerability in a transitional age youth (age 18–25) sample, as compared to a matched general adult sample, for treatment-resistant depression [152], suggesting no differences in response by age. Therefore, all these finding

Table 2
Clinical and preclinical evidences supporting the use of ketamine in adolescence.

REFERENCE	CLINICAL SUBJECTS	TREATMENT	OUTCOME	SIDE EFFECTS
[153]	Thirteen adolescents (12-18 years old) with TRD	Intravenous ketamine 0.5 mg/kg, 6 infusions over the course of 2 weeks	Improvement of depressive symptoms (CDRS-R) in 38% of subjects; 3 participants went into remission	Changes in blood pressure, dysphoria, dissociative state (CADSS) and nausea
[154]	Seventeen adolescents (13-17 years old) with TRD	Single dose of ketamine 0.5 mg/kg over 40 min vs. midazolam 0.045 mg/kg over 40 min	Reduction of depressive symptoms 24 h post-infusion (MADRS and CDRS-R); antidepressant effect 14 days post-infusion (MADRS)	Changes in systolic blood pressure, transient dissociative symptoms (CADSS)
[155]	Case report: adolescent (16 years old) with MDD, suicidal ideation, ADHD and Crohn's disease	Intravenous ketamine 0.5 mg/kg, 7 infusions over 40 min	Rapid reduction in depressive symptoms (MADRS and CDRS) and suicidal ideation (SSI)	Nausea and dissociative symptoms (CADSS)
[156]	Case report: adolescent (15 years old) with TRD and psychotic features	Intravenous ketamine 0.5 mg/kg, 6 infusions over the course of 3 weeks	Gradual reduction in depressive symptoms (MADRS and CDRS-R) and suicidal ideation (SSI)	Symptoms of derealization and nausea
[158]	Case report: adolescent (female 17 years old) with TRD and chronic suicidal ideation	Nasal spray of ketamine 28 mg, 2 x week with 2 days interval for 4 weeks, then once a week for 3 weeks	No improvement in mood; no clinically significant changes observed	Dizziness, nausea and fatigue
[159]	Four case reports: adolescents (14-19 years old) with TRD and others psychiatric disorders (anxiety, panic attack, eating disorders…)	Ketamine-assisted psychotherapy; sublingual ketamine (100-200 mg), then intramuscular ketamine (50-100 mg)	Symptomatic and functional improvements (BDI and HAMD)	Dissociative effects, numbness, walking difficulty, nausea and sleep disturbances
[160]	Fifty-four adolescents (13-18 years old) with anxious and non-anxious MDD	Intravenous ketamine 0.25 mg/kg vs. midazolam 0.045 mg/kg, 3 infusions over 5 days	Improvements in suicidal ideation in the non-anxious group (C-SSRS); similar antidepressant effects in both groups; higher remission rate in the non-anxious group 4 weeks post-treatment (MADRS)	Moderate dissociative effects (greater severity in anxious group)
[161]	Fifty-four adolescents (13-18 years old) with MDD and suicidal ideation	Intravenous ketamine 0.25 mg/kg vs. midazolam 0.02 mg/kg, 3 infusions over 5 days	Improvements in suicidal ideation (C-SSRS) and depressive symptoms (MADRS)	Nausea, dissociative symptoms, dry mouth, dizziness and headache
[168]	Male Sprague-Dawley adolescent (PND 35) rats: control vs. CUS	Ketamine i.p. (0, 5, 10 and 20 mg/kg), 1 or 15 consecutive days	Acute dose of 20 mg/kg: antidepressant-like effects in FST and reverse depressive-like phenotype CUS 24 h post-injection	Repeated treatment dose of 20 mg/kg: reduce food intake and weight gain
[169]	Male and female Sprague-Dawley adolescent (PND 33-39) rats: control vs. MD	Ketamine i.p., 5 mg/kg, 7 consecutive days, 1 dose per day	Acute antidepressant-like effects in naïve male (30 min post-injection) and female maternal deprived rats in FST and repeated antidepressant-like effects in NSF (24 h post-last injection)	Not evaluated
[170]	Male and female Sprague-Dawley adolescent (PND 33-39) rats	Ketamine i.p. (1, 5 and 10 mg/kg) for 7 consecutive days	Acute dose of 10 mg/kg: antidepressant-like effect in female rats (FST)	No significant long-term changes in cognition (Barnes maze)
[171]	Male C57BL/6 J adolescent (PND 35) mice: control vs. CSDS	Ketamine i.p. (0, 5, 10 and 20 mg/kg)	Dose of 10 mg/kg: antidepressant-like effects (FST and SI). Repeated treatment (10 mg/kg) produces a stress-resistant phenotype (FST and SI)	Not evaluated
[172]	Female Wistar adolescent (PND 25) rats	Ketamine i.p. (10 mg/kg), intermittent administration (3 days ON followed by 4 days OFF)	Anxiogenic and depressive profile (OF, EPM and FST)	Mnemonic impairment (inhibitory avoidance task) and oxidative stress state
[181]	Male Sprague-Dawley adolescents (PND 35) rats	Ketamine i.p. (25 mg/kg), 10 consecutive days	Evaluated the potential side effects induced by ketamine exposure during adolescence	Changes in locomotor activity during adolescence; no cognitive deficits observed

Abbreviations: BDI: Beck's depression inventory; CADSS: clinician-administered dissociative states scale; CDRS: children's depression rating scale; C-SSRS: Columbia suicide severity rating scale; CUS: chronic unpredictable stress; CSDS: chronic social defeat stress; EPM: elevate plus maze; FST: forced swim test; HAMD: Hamilton depression rating scale; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; NSF: novelty-suppressed feeding test; OF: open field; PND: postnatal day; SI: social interaction; SSI: scale for suicide ideation; TRD: treatment-resistant depression.

should encourage further research into the use of ketamine as a novel antidepressant for adolescent depression.

As mentioned earlier, although clinical studies are limited for this age group, overall, the data point to the administration of ketamine as an efficacious treatment for decreasing depressive symptoms in adolescent patients with treatment-resistant depression and/or suicidal ideation (see Table 2 for more details). In a first clinical trial, intravenous ketamine (0.5 mg/kg x 6 times over the course of 2 weeks) administered to adolescents (12–18 years old) with treatment-resistant depression induced promising antidepressant effects observed several weeks post-treatment [153]. However, the response rate was 38%, a lower rate than the one observed for adults, plus 3 of the participants went into remission [153], and contrary to what was just described, these results suggested that ketamine might actually present diminished efficacy in adolescence. Later on, a proof-of-concept randomized, double-blind, single-dose crossover clinical trial, showed that one intravenous dose of ketamine (0.5 mg/kg) in adolescents with depression was well tolerated acutely while proved better short-term (2-week) efficacy in reducing depressive symptoms than the standard midazolam [154]. In addition, several case reports showed improved depressive symptoms when ketamine was administered repeatedly to treat adolescent patients diagnosed with treatment-resistant depression with suicidal behaviors in combination with other psychiatric disorders such as psychosis or anxiety (e.g., [155,156]). A recent review summarized all these studies [157].

In addition to all this data, during these past months of 2023, several new studies evaluating the potential use of ketamine for adolescent depression have been published. In particular, in one clinical case with a 17-year-old female adolescent suffering from treatment-resistant depression, ketamine (through intranasal application) did not demonstrate effectiveness [158]. However, 3 other studies showed promising results [159–161]. The first one reported the data from 4 cases of adolescents aged 14–19 with multiple psychiatric diagnoses (but all including treatment-resistant depression) and treated with sublingual ketamine, followed by sessions with intramuscular ketamine [159]. The results showed that each case showed symptomatic and functional improvements, treatments were well-tolerated, and the involvement of families seemed essential to treatment success [159]. The second study aimed at comparing the efficacy of esketamine in adolescents with major depressive disorder and suicidal ideation, both anxious or non-anxious [160]. The results showed that intravenous esketamine (3 infusions), together with a routine inpatient care and treatment, better improved immediate post-treatment anti-suicidal behavior in adolescents with non-anxious depression than in those with anxious; although the effects were transient and not sustained [160]. Finally, and more promisingly, the latest preliminary results of a randomized active-placebo-controlled trial in 54 adolescents (aged 13–18) indicated that a 3-dose intravenous paradigm of esketamine, together with the routine inpatient care and treatment, was effective and well-tolerated for treating adolescents with major depressive disorder and suicidal ideation [161]. Moreover, besides all these published studies, there are several ongoing active clinical trials further characterizing the effects of ketamine for treatment-resistant depression in adolescence that will soon provide more details in terms of efficacy and safety (https://www.clinicaltrials.gov/search?cond=Treatment%20Resistant%20Depression&term=Adolescent&intr=Ketamine&limit=100&page=1).

Generally, these initial studies suggested that ketamine exerts rapid-acting antidepressant effects in adolescent patients with treatment-resistant depression and may also reduce suicidal ideation. The variability observed in ketamine's efficacy between age groups (adulthood vs. adolescence), with an apparent lower response rate in adolescence, could be due to the duration of the treatment and/or the route of administration of the drug, since a nasal spray was always used in adulthood while an intravenous infusion was the most form of administration used in adolescent clinical trials. Besides, the onset of a depressive disorder during the early stages of development has been associated with a more severe symptomatology (reviewed by [162]), which might explain the need for a more extensive treatment and/or higher doses of ketamine during adolescence to match the efficacy observed in adulthood. Interestingly, the potential negative effects induced by ketamine, which seem to be mild and disappear hours after treatment, are similar for different age ranges and include transient dissociative effects, nausea and vomiting (e.g., [151]). In any case, to answer the issues concerning the safety of ketamine's administration in the rapidly developing brains of adolescents, we will need a better description of the possible long-term adverse effects emerging in adulthood following adolescent treatment. Moreover, given the described sex differences in treatment response for certain antidepressants (see [33–35]), and for ketamine in particular (e.g., [147]), although some prior studies did not report sex-differences particularly for this drug in adulthood [163,164] (see review by [165], it would necessary to include both sexes when further characterizing its effects for adolescence in all preclinical studies, as well as to include sex as a potential variable in future clinical trials.

3.1.2. Further preclinical characterization in adolescence

Preclinical studies evaluating the antidepressant-like efficacy of ketamine started booming around the year 2000, though most of these studies were conducted in adult male animals. The firsts experiments evaluating ketamine's effects in adolescent rodents are more recent (see review [166] and [167,168] among other studies; see Table 2 for more details), including some experiments of our own [169,170]. In general, when revising the preclinical studies, one could conclude that while most experiments showed the antidepressant-like effects of acute ketamine at sub-anesthetic doses, the results were highly variable and seemed to depend on several factors, such as dose administered, duration of treatment, sex and/or species/strains of animals used. In fact, some controversy exists regarding the dose of ketamine needed to induce an acute antidepressant-like effect in adolescence, with some reports suggesting a dose range between 10–20 mg/kg, higher than the one needed in adulthood (e.g., see review [166] and [167]), while others used lower doses (5 mg/kg; [169]). On the other hand, when revising the effects after repeated ketamine treatment, the results are sensitive in terms of its beneficial vs. potentially harmful effects based on the dose administered. For example, and in line with previous studies demonstrating antidepressant-like effects induced after chronic ketamine treatment (e.g., [168,171]), a recent study from our group proved that a 7-day repeated treatment with ketamine induced an antidepressant-like effect in adolescent rats that lasted up to 3 days post-treatment [169]. Contrarily, another study with higher doses of repeated ketamine showed long-term pro-depressant-like effects in female rats [172]. Furthermore, prior studies have centered in evaluating the differential effects of ketamine as influenced by sex; while some studies in rodents reported improved responses for females [167,173–174] or males [175] (please note that references 173–175 were studies done in adult rodents), others showed that while there were no sex differences in efficacy, this was dependent on prior early-life stress exposure [169]. Therefore, from the previously described adolescent data, together with experiments performed in adult rodent models [176–180], we could conclude that the antidepressant-like effects of ketamine are dependent on factors such as sex, age, and prior stress exposure (e.g., [168–169, 176–178]), as well as the potential dose-related actions behind these disparities [133,171,179,180].

Overall, the results suggest that ketamine is a good pharmacological option for the fast-acting treatment of adolescent depression. Future studies should center in evaluating possible negative effects emerging later on in adulthood, such as drops in efficacy after repeated schedules of administration, cognitive changes, and/or its addictive potential (e.g., [181]). In this context, a previous study from our group demonstrated a certain drop in efficacy when ketamine was re-administered in adulthood in rats previously treated in adolescence, proving the need for future higher doses and/or longer treatments in adulthood to induce the

expected antidepressant-like response [169]. Our ongoing studies demonstrated no long-term effects in adulthood following adolescent ketamine exposure (a dose response study for both sexes) both in cognitive performance and rewarding properties of the drug, proving a good long-term safety profile [170].

3.2. Classical psychedelics

Classical psychedelics are a group of compounds that stand out for inducing antidepressant effects similar to those of ketamine, but with a different pharmacological target (reviewed by [182]). Classical psychedelics such as psilocybin, LSD, MDMA or mescaline have a very complex molecular correlate, but several animal studies have demonstrated the important role of serotonin 2 A receptors (5-HT2AR) in their mechanism of action [183] (reviewed by [184]). It seems that 5-HT2ARs are related to the observed antidepressant-like effects and to the psychoactive effects they induce, such as hallucinations (e.g., [185]). 5HT2AR agonism increases serotonin levels and excitability of pyramidal neurons of the cortex, rising glutamate levels and the after activation of the corresponding signaling pathways, such as the promotion of synaptic plasticity processes [184,186].

Although a few clinical trials are currently underway to evaluate the antidepressant-like potential of psilocybin for adult patients (see link: https://www.clinicaltrials.gov/search?cond=Treatment%20Resistant%20Depression&intr=Psilocybin), including some preliminary published results [187], no studies are yet being conducted in adolescence and therefore the information available on this topic is very limited. Overall, although exclusively based on preliminary data in adulthood [128,131], psychedelic therapies seemed like a good option to be explored as antidepressants for adolescence, but not before further preclinical and clinical research is done.

4. Cannabinoids: cannabidiol and other compounds

Cannabis sativa is currently one of the most popular recreational and medicinal plants, with many active phytocannabinoids as the main components providing several beneficial properties. The endocannabinoid system plays important roles in mainly all parts of our body, through the facilitation of key processes of central and peripheral disorders, and/or represents a key therapeutic target for treatment (e.g., [188,189]). In this context, a recent book was just published summarizing the use of cannabis and/or cannabinoids in a variety of medical conditions (see [190] among many others covering this hop topic). In terms of its medicinal use, the most studied active components are Δ9-trans-tetrahydrocannabidiol (THC) and cannabidiol. Specifically, the clinical benefits of these cannabinoids have been mainly centered in neurological disorders (e.g., epilepsy or Parkinson) or pain management for cancer patients (e.g., [189]), and lately in mood disorders, since the regulation of the endocannabinoid signaling with certain pharmacological agents showed positive effects on affect (reviewed by [191,192]). In particular, while THC is recognized as the compound responsible for the psychoactive and intoxicating effects of the plant, cannabidiol is a non-psychotomimetic component with several putative clinical applications [193,188–189], including an antidepressant-like potential [194–201]. Interestingly, cannabidiol seems to present no risk of causing dependence after repeated use [202] and lacks toxicity in animals and humans [203]. For this reason, among all cannabinoids in the plant, the searchlight for novel fast-acting antidepressants for adolescent depression has been directed mainly to the potential use of cannabidiol.

4.1. Cannabidiol

Cannabidiol is currently exclusively approved for certain types of resistant epilepsy (when given in monotherapy), or certain types of chronic pain (when combined with THC). Specifically, the registered compounds are Epidiolex, an oral cannabidiol solution, which is used as an adjunctive treatment in patients with Lennox-Gastaut syndrome or Dravet syndrome in children, and Sativex, an oral spray of THC and cannabidiol, currently available in Canada for the symptomatic relief of spasticity and neuropathic pain in adult patients with multiple sclerosis, as well as moderate/severe pain in patients with advanced cancer (e.g., [189]). Besides epilepsy, cannabidiol has shown indications of efficacy for the treatment of different disorders such as depression, anxiety and psychosis [204,205]. Interestingly and despite the fact that cannabidiol is already approved for certain clinical uses, its mechanism of action is not fully elucidated, and is hypothesized to include a wide range of molecular targets and a very complex pharmacological profile (see [203, 206] among several others). In particular, while cannabidiol seems to act as a negative allosteric modulator with low affinity to the cannabinoid receptors (CB1 and CB2), it is capable of increasing anandamide through the inhibition of fatty acid amide hydrolase, and can act on other systems, such as the serotonergic system (an allosteric modulator of the 5-HT1A receptor), the TRPV1–2 receptor system, or the GPR receptor family (GPR3, GPR6, GPR12, GPR55), which are G protein-coupled receptors (reviewed by [205,207]).

A huge effort has been made in the past years to characterize the antidepressant-like effects of cannabidiol [194–201], although mainly at the preclinical level, since there are no clear clinical evidences supporting its use in humans for major depressive disorder. One of the main causes of reported self-medication with cannabidiol seems to be to improve depressive-like symptoms (e.g., [208–210]; for more information see [211]). However, there are no randomized controlled clinical trials that study cannabidiol as a treatment for major depression [211]. In fact, when searching in ClinicalTrials.gov for clinical trials utilizing cannabidiol for major depression, only 7 results came up (https://clinicaltrials.gov/search?cond=depression&term=cannabidiol). The most relevant study, which aimed at evaluating the potential use of cannabidiol for treatment resistant depression was withdrawn in the year 2021 due to lack of funding (see link to the study: https://clinicaltrials.gov/ct2/show/NCT04732169). The rest of studies are mainly oriented to bipolar depression and are therefore not directly relevant to the current revision. In fact, the few clinical evidences present in the literature have centered in exploring the improvements of depressive symptoms (among other related variables, such as anxiety or insomnia) associated with another pathological process, mainly chronic or neuropathic pain, instead of the effects of cannabidiol "per se" in patients with major depression. Plus, the treatments normally included a cannabis-based medicinal product, which could typically be either pure cannabidiol, pure THC, or a combination of both [212–214]. In the same line of results, a prior observational study showed improved depressive-like symptoms as measured 1-, 3- and 6-months post-treatment in patients with treatment-resistant depression, but mediated by a cannabis-based medicinal mixture rather than just cannabidiol alone [215]. Therefore, up to date, there are no clinical studies supporting the use of cannabidiol as an antidepressant in the context of depression (treatment resistant or not). Contrarily, there are several clinical trials evaluating the effects of cannabidiol for anxiety, post-traumatic stress disorder or insomnia (e.g., reviewed by [194]). Overall, there is an evident need for more clinical investigation towards the potential use of cannabidiol as a treatment alternative in patients with depression, and even more so for adolescent patients.

4.1.1. Clinical evidence for its use in adolescence

Unfortunately, there are almost no studies evaluating the antidepressant-like potential of cannabidiol for adolescent patients with major depression (see Table 3 for details on the few studies available). It is worth highlighting a recent clinical case in which an oral cannabidiol treatment (100–600 mg/day, for 8 weeks) was capable of improving the symptoms observed in an adolescent (17 years) with multiple substance use disorder, depression, social phobia and narcissistic personality disorder [195]. Moreover, two recent studies have also evaluated the improvement of anxiety symptoms in adolescents with

Table 3
Clinical and preclinical evidences supporting the use of cannabidiol in adolescence.

REFERENCE	CLINICAL SUBJECTS	TREATMENT	OUTCOME	SIDE EFFECTS
[195]	Adolescent patient (17 years old) with substance abuse disorder, severe depression, social phobia and narcissistic personality disorder	Cannabidiol capsules (100-600 mg/day, for 8 weeks)	Improvement of depressive and anxiety symptoms (Beck Depression Inventory II and the German version of the Fear Survey Schedule for Children), simple phobias, and symptoms of paranoia and dissociation	Not reported
[196]	Thirty-one adolescent and/or young adults (12-25 years old) with anxiety disorder	Cannabidiol (800 mg/day, for 12 weeks)	Improvement of anxiety severity and comorbid depressive symptoms (CGI score)	Fatigue, low mood, and hot flushes or cold chills (in 15 of 31 participant)
[197]	Thirty-seven teenagers (18-19 years old) with social anxiety disorder and avoidant personality	Cannabis oil (containing 300 mg of cannabidiol, daily, for 4 weeks)	Improvement of anxiety symptoms (FNE and LSAS)	Not evaluated
[169]	Male and female Sprague-Dawley adolescent (PND 33-39) rats: control vs. MD	Cannabidiol i.p., 10 mg/kg, 7 consecutive days, 1 dose per day	Acute antidepressant-like effects in naïve male (30 min post-injection) in FST; repeated effect (24 h post-last injection) in FST and NSF. No effects on female rats	Not evaluated
[26]	Male Sprague-Dawley adolescent (PND 27-33) rats	Cannabidiol i.p. (3, 10, 30 mg/kg), 7 consecutive days, 1 dose per day	Repeated dose of 10 mg/kg: antidepressant-like effect in FST (2 days post-treatment)	Not evaluated
[201]	Male Sprague-Dawley adolescent (PND 33-39) rats with MD	Cannabidiol i.p. (10 mg/kg), 7 consecutive days, 1 dose per day	Antidepressant effect in the NSF (4 days post-treatment)	Not evaluated
[216]	Male CD1 adolescent (PND 28-48) mice	Cannabidiol + THC 3 mg/kg each, 20 consecutive days, 1 injection per day	Prevention of THC-induced behavioral abnormalities (NOR, Nestlet shredding, Marble burying, EPM)	Not evaluated
[217]	Male and female C57BL/6 J adolescent (PND 25-45) mice	Cannabidiol i.p. (20 mg/kg), 21 consecutive days, 2 injections per day	Evaluated the potential long-term effects induced by cannabidiol exposure during adolescence	No negative impact on a range of behaviors in adulthood: e.g., improvement in spatial memory task (Barnes maze)
[218]	Male Wistar adolescent (PND 30-44) rats	Cannabidiol i.p. (5, 30 mg/kg), 14 consecutive days, 1 dose per day	Evaluated the potential long-term effects induced by cannabidiol exposure during adolescence	Influence on the sleep-wake cycle
[219]	Female Sprague Dawley adolescent (PND 35-45) rats	THC-rich/cannabidiol poor, cannabidiol-rich/THC-poor, i.p., 10 days, 2 injections per day	Evaluated the potential long-term effects induced by cannabidiol exposure during adolescence	Short-term memory deficits and/or anhedonia in adult female rats, related mainly with THC

Abbreviations: CGI score: clinical global impressions scale; EPM: elevated plus maze; FNE: fear of negative evaluation questionnaire; FST: forced swim test; LSAS: Liebowitz social anxiety scale; MD: early-life maternal deprivation; NOR: novel object recognition; NSFT: novelty-suppressed feeding test; PND: post-natal day; THC: tetrahidrocannabinol.

treatment-resistant anxiety disorder [196] or social anxiety [197]. In the first study, thirty-one young people (aged 12–25 years old) were treated with 800 mg/day of cannabidiol for 12 weeks and, in the second study, seventeen 18–19 years old Japanese teenagers were treated with cannabis oil containing 300 mg of cannabidiol for 4 weeks. Again, and as observed for the adult studies, either the clinical study was not exclusively directed for major depressive disorder, or the drug used contained other compounds besides cannabidiol, making it impossible to conclude anything related to the potential use of cannabidiol as an antidepressant for adolescent depressed patients. Up to date, a lot of clinical data is still needed for cannabidiol to eventually be accessible in the clinic for adolescent depressed patients. Future clinical trials should also include sex as a biological variable, as most prior studies did not report improvements according to sex, while also aim at comparing cannabidiol's efficacy by age (adult vs. adolescent patients), since prior reports only included patients older than 18 years. Interestingly, cannabidiol has already proven great efficacy and safety during adolescence, although in young patients with treatment-resistant epilepsy. Therefore, repurposing this drug for treatment-resistant depression could take advantage of these years of acquired knowledge in another medical field for young patients.

4.1.2. *Further preclinical characterization in adolescence*

For the past decades, preclinical researchers have been depicting the potential use of cannabidiol to improve affective-like behavior, including its antidepressant-like response [194,198–201]. In general, all the preclinical data published up to date seem to corroborate an antidepressant-like response of cannabidiol, although the magnitude of its therapeutic effect is dependent on several factors, such as strain and/or species used, biological sex, prior exposure to early-life stress, and/or treatment duration, dose and/or route of administration. In general, cannabidiol is capable of inducing a fast-acting antidepressant-like response, since effects were observed right after a single dose [169], but also a sustained one, which was observed up to several

days after a repeated treatment (e.g., [26]). The most commonly used and beneficial effective doses are 10 mg/kg and 30 mg/kg (for more details see Table 3). However, most of these studies mainly focused on the behavioral and neurochemical effects exerted by cannabidiol in adult male rodents, excluding potential sex differences in the response induced by the drug (note that Table 3 only includes original preclinical studies performed in adolescent rats). Of the few studies that have evaluated the effects of cannabidiol including both sexes, it is concluded that the drug induces a differential effect in female rodents, and while some reported certain efficacy (e.g., [198]), others mostly showed a lack of efficacy in females at similar doses tested in males [169,199,200].

As for the potential effects of cannabidiol in adolescence, most of the available published data is from our research group. Our first study aimed at comparing in male rats the effects of a dose-response treatment with cannabidiol (3, 10 and 30 mg/kg) in adolescent and adult rats [26]. The main results showed that a repeated 7-day treatment with cannabidiol was efficacious both in adolescence and adulthood, but at different doses (10 mg/kg for adolescence and 30 mg/kg for adulthood) and with a different length in response (2 days in adolescence vs. 21 days post-treatment in adulthood), proving a long-term response of cannabidiol after treatment, especially in adulthood, while suggesting a decrease potential for adolescence [26]. Moreover, the results observed in male adolescent rats were validated in a separate study, in which cannabidiol also exerted antidepressant-like effects during adolescence in a rat model of early-life stress [201]. Our follow up study included adolescent rats of both sexes, previously exposed or not to maternal deprivation (as a model of early-life stress) and evaluated both potential fast-acting and long-term antidepressant-like responses [169]. In male adolescent rats, the results showed that cannabidiol induced both rapid and sustained antidepressant-like effects in naïve rats, while needed a repeated regimen exposure to be able to produce an antidepressant-like response in maternally deprived rats [169], suggesting that stress increases the dose needed for cannabidiol to be efficacious. In female adolescent rats, contrarily, cannabidiol did not exert an antidepressant-like response [169], in line with prior results done in adult rodents [199,200]. In this regard, we are currently investigating the potential sex-driven mechanisms behind the observed disparities in the response induced by cannabidiol in adolescence.

As mentioned earlier, when evaluating the effects of novel treatment options for adolescent depression, it is important to also consider potential long-term changes in efficacy and/or long-term safety (e.g., changes in cognitive performance). In this context, our study demonstrated a certain drop in adulthood efficacy following a prior treatment with cannabidiol in adolescence, showing that in this particular scenario prolonged treatments (and/or increased doses) would be needed to observe an antidepressant-like response in adulthood [169]. Other interesting studies have evaluated the possible long-term effects of adolescent cannabidiol exposure on some aspects of anxiety, sleep deprivation and memory (e.g., [216–219] and Table 3). In particular, adolescent cannabidiol induced a long-term improvement on the learning rate of a spatial memory task [217], and was able to prevent all THC-induced behavioral abnormalities, related with memory, repetitive and compulsive-like behaviors and anxiety in adolescent male CD1 mice [216]. Although, in general, cannabidiol did not display severe long-term consequences following an adolescent treatment, in terms of locomotion and/or anxiety-like behaviors [217], it influenced the sleep-wake cycle in adult rats [218], together with the development of short-term memory deficits and/or anhedonia in adult female rats (though treated with a chronic cannabidiol-THC combined treatment) [219]. Future studies should center in further depicting the long-term changes induced by adolescent cannabidiol exposure while including both sexes. In this regard, we just finished analyzing some preliminary data (yet to be published) demonstrating no long-term impact on cognitive performance as measured in the Barnes maze in adult rats of both sexes previously exposed to different doses of cannabidiol (up to 60 mg/kg) during adolescence (personal communication).

Based on the data presented, it is clear that cannabidiol displays antidepressant-like properties in adolescence, although the magnitude of its therapeutic response depends on several factors, such as biological sex, prior stress exposure, etc., and therefore deserves further characterization. The promising preclinical data presented should encourage future well-design clinical trials to move forward this drug as a fast-acting antidepressant for adolescent depression, especially given its known safety profile for this particular age population.

4.2. Other cannabinoids

Searching the literature, we could only find a previous study comparing the antidepressant-like effects of several cannabinoids in male mice. The results showed that the cannabinoids cannabigerol and cannabinol did not produce antidepressant-like actions up to 80 mg/kg in the mouse forced-swim test, while cannabichromene and cannabidiol (in line with the previously exposed results) exhibited significant effects at 20 and 200 mg/kg, respectively [220]. Although this study suggested no antidepressant-like potential for cannabigerol, further studies will need to fully describe its effects while including other species and both sexes. This is especially relevant, since cannabigerol, which is also a non-psychotropic component of *Cannabis sativa*, is attracting increasingly therapeutic attention in many fields (see [221] for more information). Moreover, since this is a relatively new topic, both preclinical and clinical studies are still missing in the context of the ascertaining the real potential use of other cannabinoids, besides cannabidiol, for adolescent depression.

In general, all these compounds display low affinity for cannabinoid receptors, as it is hypothesized that their antidepressant-like potential, among other effects such as the ones exerted for the treatment of cancer or neurodegenerative diseases, are driven by other mechanisms of action. For example, cannabigerol is the precursor of cannabidiol and THC and it inhibits anandamide uptake, increasing the levels of this endocannabinoid. Moreover, cannabigerol can act on TRPV1, a receptor that has been related to depression, making it a potentially good candidate for the treatment of this disease [222]. Thus, although this field of study has not yet been developed, it would be interesting to conduct further research to use cannabinoids as therapeutic tools for depression.

5. General conclusions and future directions

In this review we have presented novel rapid-acting options to be further develop for its use in treatment-resistant adolescent depression and/or suicidal ideation. In particular, we have described both non-pharmacological options such as neuromodulators (electroconvulsive therapy and other types of brain stimulation), as well as pharmacological options, including consciousness-altering drugs (mainly ketamine but also classical psychedelics) and cannabinoids (i.e., cannabidiol). The most advanced and/or feasible options to be implemented in the clinic seem to be electroconvulsive therapy and ketamine, specially, since electroconvulsive therapy is already in use for particular situations in adolescence, and some preliminary clinical data is available for the use of adolescent ketamine. In fact, several reviews and meta-analysis have compared the efficacy of electroconvulsive seizures with ketamine for treatment-resistant depression in adult patients, and while some suggested better outcomes for electroconvulsive seizures (e.g., [57]) others found no differences (e.g., [223]), or even superior responses for ketamine (e.g., [224]). Therefore, if one would expect similar outcomes in adolescence, both approaches should be good alternatives for treatment-resistant depression. On the other hand, cannabidiol's use for adolescent depression still requires further studies and clinical characterization for this particular age group. In any case, the end goal of all these options would be to generate treatment guidelines focused on treatment optimization for psychiatric conditions known to be associated with suicide risk (reviewed by [225]). Moreover, given the nature of these novel therapeutical options, certain ethical considerations

would need to be considered before its use in clinical treatments (i.e., informed consent, role of expectancy in clinical response, distributive justice, etc.) [140].

In this context, we need to better understand the optimal doses for each approach, treatment condition, and biological sex, as well as the long-term impact that these adolescent treatments (in still developing brains) would generate in adulthood in terms of future therapeutical needs and/or safety. Moreover, future studies should center in finding the converging mechanisms for these fast-acting antidepressants since a greater understanding of the underlying mechanisms by which these potential novel treatment options might induce fast-acting efficacy in adolescence will be key to further comprehend the particular neurobiology behind adolescent depression and its treatment, and/or to develop novel interventions. One mechanism that seems common to most antidepressants, at least to the ones described in this review, is centered in hippocampal plasticity through the potential role of hippocampal BDNF and subsequent signaling via TrkB receptors (e.g., [226]) as a key mediator of antidepressant action [227–232] (see Fig. 1 for a schematic diagram of their putative common mechanism of action, and see [233] for our own data reporting the regulation of BDNF by electroconvulsive seizures in adolescent rats of both sexes). In conclusion, the future clinical use of these therapeutical approaches looks really promising for the faster treatment of adolescent depression, besides the current use of the only few safe classical antidepressants available.

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Authors contribution statement

M.J.G.-F. guided the scope and conceptualization of this review article. S.L.-C. drafted the part on neuromodulators, J.J.-P. on consciousness-altering drugs, and L.G.-M. on cannabinoids. M.J.G.-F. wrote the rest of the manuscript and edited all parts to their final versions. All authors critically revised the manuscript.

CRediT authorship contribution statement

Gálvez-Melero Laura: Writing – original draft, Writing – review & editing. **Garcia-Fuster M. Julia:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **Ledesma-Corvi Sandra:** Writing – original draft, Writing – review & editing. **Jornet-Plaza Jordi:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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