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Psychopharmacology in children and adolescents: unmet needs and opportunities

Samuele Cortese, Diane Purper-Ouakil, Alan Apter, Celso Arango, Inmaculada Baeza, Tobias Banaschewski, Jan Buitelaar, Josefina Castro-Fornieles, David Coghill, David Cohen, Christoph U Correll, Edna Grünblatt, Pieter J Hoekstra , Anthony James, Pia Jeppesen, Péter Nagy, Anne Katrine Pagsberg, Mara Parellada, Antonio M Persico, Veit Roessner, Paramala Santosh, Emily Simonoff, Dejan Stevanovic, Argyris Stringaris, Benedetto Vitiello, Susanne Walitza, Abraham Weizman, Ian C K Wong, Gil Zalsman, Alessandro Zuddas, Sara Carucci, Florence Butlen-Ducuing, Maria Tome, Myriam Bea, Christine Getin, Nina Hovén, Asa Konradsson-Geuken, Daphne Lamirell, Nigel Olisa, Begonya Nafria Escalera, Carmen Moreno

Psychopharmacological treatment is an important component of the multimodal intervention approach to treating mental health conditions in children and adolescents. Currently, there are many unmet needs but also opportunities, alongside possible risks to consider, regarding the pharmacological treatment of mental health conditions in children and adolescents. In this Position Paper, we highlight and address these unmet needs and opportunities, including the perspectives of clinicians and researchers from the European College of Neuropsychopharmacology–Child and Adolescent Network, alongside those of experts by lived experience from national and international associations, via a survey involving 644 participants from 13 countries, and of regulators, through representation from the European Medicines Agency. We present and discuss the evidence base for medications currently used for mental disorders in children and adolescents, medications in the pipeline, opportunities in the development of novel medications, crucial priorities for the conduct of future clinical studies, challenges and opportunities in terms of the regulatory and legislative framework, and innovations in the way research is conducted, reported, and promoted.

Introduction

The peak age of onset across mental disorders is bimodal, with early onset conditions such as neurodevelopmental disorders peaking in childhood (ie, age <12 years), and later onset disorders peaking in adolescence (ie, age 12–17 years) and young adulthood (ie, age 18–25 years), with onset before the age of 18 years occurring in around 50% of cases.[1] Preventive and treatment strategies in childhood and adolescence are crucial to decrease the burden of mental illness, and pharmacotherapy is a key component in the multimodal strategy for managing mental health conditions in children and adolescents.

International pharmaco-epidemiological data point to increased use of psychotropic medications for children and adolescents (age <18 years) in the past two decades. In a study across 65 countries,[2] the total psychotropic medication sales for children and adults increased from 2008 to 2019, with a relative average annual increase of 4·08% (95% CI 2·96–5·21). Other international studies have shown increases in specific psychotropic use in children and adolescents, including ADHD medications[3] and antidepressants.[4]

High unmet needs and opportunities remain, alongside possible risks to consider. Relatively few medications are licensed for children and adolescents, with most medications still being tested first in adults, which limits and delays access to medications for children and adolescents. There is also limited evidence about the developmental impact of psychotropics. Although increases in the consumption of psychotropics by children and adolescents might relate to a perceived increase in need, it could also be accounted for by poor or variable access to other treatments (eg, evidence-based psychotherapy), which might be as or more effective for some conditions. Medications might be either not prescribed for appropriate indications or prescribed in situations where there is no evidence for effectiveness and safety.

Following a review[5] by the European College of Neuropsychopharmacology–Child and Adolescent Network (ECNP–C&A) on unmet needs in child and adolescent psychopharmacology, this international Position Paper is the first, to our knowledge, to address unmet needs and opportunities in the field, including not only the perspectives of clinicians and researchers from the ECNP–C&A, but also those of experts by lived experience and regulators, through representation from the European Medicines Agency (EMA). The methodology underpinning this paper is reported in panel 1. Given the composition of our group, the present paper has predominantly a European focus, but the network also includes members working outside of Europe.

Current situation

Psychotropic medications

Psychopharmacological medications approved as of June 2023, by the EMA in Europe and the Food and Drug Administration (FDA) in the USA, for mental health conditions in children and adolescents are reported in table 1. This list reflects only a small proportion of medications approved for mental health conditions in children and adolescents in Europe, because companies can apply for registration nationally rather than to the EMA. Furthermore, many medications were licensed before the establishment of the EMA in 1995. However, EMA monitors the safety and efficacy of drugs even when not approved centrally and can take actions on them if necessary.

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Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, and Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK (Prof S Cortese MD); **Solent NHS Trust, Southampton, UK** (Prof S Cortese); **Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York City, NY, USA** (Prof S Cortese); **Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK** (Prof S Cortese); **DiMePRe-J-Department of Precision and Regenerative Medicine-Jonic Area, University of Bari "Aldo Moro", Bari, Italy** (Prof S Cortese); **Centre Hospitalo-Universitaire de Montpellier, Service Médecine Psychologique de l'Enfant et de l'Adolescent, Montpellier, France** (Prof D Purper-Ouakil PhD); **INSERM U 1018, CESP, Psychiatrie du développement – Evaluer et traiter les troubles émotionnels et du neurodéveloppement (ETE-ND), Villejuif, France** (Prof D Purper-Ouakil); **Schneider Children's Medical Center of Israel, Petach Tikva, Israel** (Prof A Apter MD); **Ivcher School of Psychology, Reichman University, Herzliya, Israel** (Prof A Apter); **Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IiSGM, CIBERSAM,**

Panel 1: Methodology

This Position Paper summarises the unmet needs and opportunities in terms of the psychopharmacological treatment of child and adolescent mental health conditions put forward by the members of the European College of Neuropsychopharmacology–Child and Adolescent Network (ECNP-C&A), alongside experts by lived experience who are representatives of the following associations: ADHD Europe, ADHD Germany, Hypersupers TDAH France, European Federation of Associations of Families of People with Mental Illness (EUFAMI), and Global Alliance of Mental Illness Advocacy Networks–Europe (GAMIAN Europe); as well as members of the Patient Engagement in Research Department of Institut de Recerca Sant Joan de Déu and representatives of the European Medicines Agency (EMA). Initially, each member of the ECNP–C&A was asked by authors SC and CM to generate a list of unmet needs and priorities. These were then grouped by topic by SC and CM and listed in an initial outline draft that was circulated to the ECNP–C&A, experts by experience representatives (parents and their children), and EMA representatives. SC, CM, and DPO held meetings with experts by lived experience and EMA representatives to discuss and refine the draft. SC, CM, and DPO then codesigned a short survey, together with experts by lived experience representatives, which was approved by the ethics committee of the University of Southampton, Southampton, UK. This survey was translated into 23 languages and circulated to the members of relevant associations located through experts by experience and ECNP–C&A members. The survey consisted of the following questions: what do you think are the most important questions on medicines for children or teenagers with mental problems that researchers should try to answer in the future? In your opinion, do people think that taking medicines for mental problems is bad? What do you think we could do to help people understand that medicines may help children and teenagers with mental problems? The initial outline draft was refined in a series of online meetings among representatives of the ECNP–C&A, associations of experts by lived experience, and the EMA. The outline was then finalised at the meeting of the ECNP-C&A (Venice, Italy, March 30, 2022), and the final draft was revised and approved by all authors and EMA representatives. To inform the Position Paper, a series of systematic searches were conducted in PubMed and Embase (last search May 13, 2023) to retrieve: any previous European or international position paper on child and adolescent psychopharmacology; international psychopharmaco-epidemiological studies including children and adolescents; umbrella reviews (ie, quantitative evidence synthesis of meta-analyses or systematic reviews) on the efficacy, effectiveness, tolerability, and safety of pharmacological interventions for child and adolescent mental health conditions; and systematic reviews on relevant compounds in the pipeline (syntax and search terms are reported in the appendix pp 1–3).

ISCIII, School of Medicine, Universidad Complutense, Madrid, Spain (Prof C Arango PhD, Prof M Parellada PhD, Prof C Moreno PhD); **Child and Adolescent Psychiatry and Psychology Department, SGR01319, Hospital Clínic de Barcelona, Neurosciences Institute, University of Barcelona, IDIBAPS, CIBERSAM-ISCIII, Barcelona, Spain** (I Baeza PhD, Prof J Castro-Fornieles PhD); **Department of Child and Adolescent Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany**

The appendix (pp 6–8) lists psychotropics currently unlicensed in Europe or by the FDA but identified by our network as commonly used off-label (ie, outside the limits of the marketing authorisation or product licence[6]). Often, but not always (eg, most medications for ADHD), medications for mental health conditions are first approved in adults, and then manufacturers can apply for an extension for children and adolescents based on the provision of sufficiently strong evidence from clinical trials or on extrapolation concepts in line with the obligatory paediatric development plan agreed with EMA or FDA. The appendix (pp 9–11) lists antipsychotics and antidepressants approved in adults via the EMA centralised procedure (a procedure for the authorisation of medicines, which is a single application, a single evaluation, and a single authorisation throughout the European Union) and the outcomes of applications for extensions to children and adolescents from 1995 to 2022. Guidelines for the EMA extension of licence and extrapolation are reported in the appendix (p 4).

The evidence base for currently used psychotropics

Over the past few decades, increasing evidence has been generated from randomised controlled trials and observational studies assessing the efficacy, effectiveness, tolerability, and safety of medications for specific disorders in child and adolescent mental health. A 2021 umbrella review[7] found the highest effect sizes in relation to efficacy for the following medications: stimulants for core symptoms of ADHD; aripiprazole and risperidone for irritability in autism spectrum disorder; risperidone for aggressiveness in disruptive behaviour disorders; risperidone, olanzapine, paliperidone, and ziprasidone for symptoms of schizophrenia; fluoxetine for depression; aripiprazole for manic symptoms in bipolar disorder; fluoxetine for anxiety disorders; fluoxetine or other SSRIs for obsessive compulsive disorder; and imipramine for enuresis.

A 2020 umbrella review on tolerability and safety[8] found the best tolerability and safety profile for escitalopram and fluoxetine, lurasidone, methylphenidate, and lithium. The most common adverse events were nausea or vomiting and discontinuation due to any adverse events for antidepressants; sedation, extrapyramidal symptoms, and weight gain for antipsychotics; decreased appetite and insomnia for stimulants for ADHD; and sedation and weight gain for mood stabilisers.

Unmet needs

With the available evidence, crucial unmet needs are evident. There are disorders for which no evidence-based or well studied pharmacological interventions are available. A survey among the members of the ECNP–C&A network identified the following disorders and conditions for which there is a need for additional pharmacological development, listed in order based on the number of votes: autism spectrum disorder (core symptoms); emotional dysregulation and irritability; anorexia nervosa and depressive disorders (with an equal score); suicidal behaviours (ie, self-harm and suicide ideation or attempts); conduct disorder and aggressiveness; addiction to drugs or alcohol; negative symptoms of schizophrenia and insomnia and other sleep disorders (with an equal score); anxiety; rare diseases such as Prader Willi syndrome; and borderline personality disorder, eating disorders other than anorexia nervosa, obsessive compulsive disorder, body dysmorphic disorder, cognitive dysfunction in intellectual disability, somatoform symptoms, and ADHD comorbid with cocaine or methamphetamine addiction (all with an equal score).

The members of the ECNP–C&A network also identified various other key unmet needs related to scarcity of evidence. First, most compounds are tested

against a placebo in single trials, creating a need for additional trials directly comparing two or more active medications as well as trials including children and young people whose symptoms do not respond or who cannot tolerate the first options. Second, by contrast with the current tendency to focus on a few core symptoms, the impact of medications on other important outcomes (eg, functional outcomes) should be explored. Third, understanding of the long-term effects (both beneficial and harmful) of psychotropic medications on the developing brain should be improved.

Additionally, a survey among experts by lived experience (644 participants from 13 countries; see panel 1) highlighted specific unmet needs from their perspective. Their responses pointed to knowledge on safety and tolerability—including the potential of medications being addictive—as the main unmet needs, alongside a need for a clear understanding of comparative effects of pharmacological and non-pharmacological interventions (table 2).

Opportunities

Medications in the pipeline

A systematic review[9] explored randomised controlled trials in phases 2 and 3 of medications for child and adolescent mental health conditions without regulatory approval, alongside randomised controlled trials of dietary interventions and probiotics, as well as phase 4 randomised controlled trials of agents targeting unlicensed indications for children and adolescents with mental health conditions. The review retrieved 234 ongoing or completed randomised controlled trials from the previous 10 years, including 26 (11%) with positive findings on one or more primary outcome, 43 (18%) with negative or unavailable results on every primary outcome, and 165 (70%) without publicly available statistical results.[9] The only two compounds with evidence of significant effects that were replicated in at least two trials without any negative trials were dasotraline for ADHD (although the developmental programme was halted by the manufacturer in 2020) and carbetocin for hyperphagia in Prader-Willi syndrome. There are opportunities for the development of novel medications or medications with a different mechanism of action. For example, the S-enantiomer of racemic ketamine, esketamine, received central approval from the EMA in 2019 for treatment-resistant depression and then the indication was extended to rapid reduction of depressive symptoms in 2021.[10,11]

Preclinical animal studies are a major sticking point in drug development, with a very small proportion (1:1000) of compounds succeeding in neuropsychopharmacology;[12] cell-based in vitro models for efficacy and safety testing could help to address these challenges while reducing the number of animals used.[13] Cell reprogramming has enabled the generation of patient-specific, induced pluripotent stem cells (iPSC) from peripheral somatic

	European Medicine Agency; age (years)	US Food and Drug Administration; age (years)
ADHD		
Amfetamine–dexamfetamine mixed salts	..	3–17
Amfetamine–dexamfetamine mixed salts extended release	..	6–17
Atomoxetine	..	6–17
Clonidine, extended release	..	6–17
Dexmethylphenidate	..	6–17
Dexamfetamine	..	3–17
Dexamfetamine sustained release	..	6–16
Guanfacine, extended release	6–17	6–17
Lisdexamfetamine	..	6–17
Methamfetamine	..	6–17
Methylphenidate	>6*†	Immediate release tablet; immediate solution; extended release (tablet, chewable); controlled delivery; multilayer extended release; extended release orally disintegrating tablets; transdermal system (6–17)
Viloxazine	..	6–17
Anxiety disorders		
Duloxetine	..	Generalised anxiety disorder (7–17)
Escitalopram	..	Generalised anxiety disorder (≥7)
Autism spectrum disorder (irritability)		
Aripiprazole	..	6–17
Risperidone	..	5–17
Bipolar disorder (depressive episodes)		
Lurasidone	..	10–17
Olanzapine–fluoxetine combination	..	10–17
Bipolar disorder (manic or mixed episodes)		
Aripiprazole	Manic episodes (≥13)	10–17
Asenapine	..	10–17
Olanzapine	..	13–17
Quetiapine extended release	..	10–17
Risperidone	..	10–17
Lithium	..	12–17‡
Conduct disorder		
Risperidone	5–18	..
Depressive disorder		
Fluoxetine	Major depressive episode unresponsive to psychotherapy† (8–18)	8–18§
Escitalopram	..	12–17
Enuresis		
Imipramine	..	6–17¶
Insomnia (in autism spectrum disorder or Smith Magenis syndrome)		
Melatonin extended release	2–18	..
Narcolepsy		
Amfetamine–dexamfetamine mixed salts	..	6–17
Dexamfetamine	..	6–17
Dextroamfetamine sustained release	..	6–17
Sodium oxybate	≥7	..

(Table 1 continues on next page)

	European Medicine Agency; age (years)	US Food and Drug Administration; age (years)
(Continued from previous page)		
Obsessive compulsive disorder		
Clomipramine	..	10–17
Fluoxetine	..	7–17
Fluvoxamine	..	8–17‖
Sertraline	6–17†	6–17
Schizophrenia		
Aripiprazole	≥15	13–17
Brexpiprazole	..	13–17
Lurasidone	≥13	13–17
Olanzapine	..	13–17
Paliperidone	≥15	12–17
Quetiapine	..	13–17
Risperidone	..	13–17
Tourette disorder**		
Aripiprazole	..	6–17

National approvals for the European countries are not included. *Approved in many individual EU countries. †Outcome after referral procedures. ‡Lithium is also indicated as a maintenance treatment for individuals with a diagnosis of bipolar disorder. §For patients aged 8–11 years the maximum approved dose is 200 mg/day; for patients aged 12–17 years the maximum approved dose is 300 mg/day. ¶For patients aged 6–12 years the approved initial dose is 25 mg once a day; for patients aged 13–17 years the approved dose is 50 mg once a day. ||For patients aged 6–11 years the approved dose is up to 50 mg/day; for patients aged 12–17 years it is up to 75 mg/day. **Pimozide is not indicated for paediatric use. Even though its use is not precluded by the US Food and Drug Administration for the treatment of Tourette disorder, it is not intended as a treatment of first choice. Haloperidol is US Food and Drug Administration approved for Tourette disorder, but it is not indicated for paediatric patients.

Table 1: **Psychotropic medications approved by the European Medicines Agency and/or by the US Food and Drug Administration for children and adolescents**

(Prof T Banaschewski PhD); **Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, Netherlands** (Prof J Buitelaar PhD)**; Karakter Child and Adolescent Psychiatry University Center, Nijmegen, Netherlands** (Prof J Buitelaar)**; Departments of Paediatrics and Psychiatry, University of Melbourne, Melbourne, VIC, Australia** (Prof D Coghill MD)**; Murdoch Children's research Institute, Melbourne, VIC, Australia** (Prof D Coghill)**; Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France** (Prof D Cohen PhD)**; CNRS UMR 7222, Institute for Intelligent Systems and Robotics, Sorbonne Université, UPMC, Paris, France** (Prof D Cohen)**; Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany** (Prof C U Correll MD)**; Psychiatry Research, Northwell**

cells (eg, blood), preserving their genetic background.[13] Such iPSCs have potential as a drug screening platform. For example, for fragile X syndrome, a proof of principle using FMR1-luciferase reporter iPSC lines, high-throughput screening, and cell viability screening showed the utility of human cell-based methods in detecting reactivators of the *FMR1* gene.[14]

Future clinical studies

The conduct of clinical trials in children and young people can be hampered by issues that can be anticipated. The European Network of Paediatric Research at the European Medicines Agency Working Group on preparedness of clinical trials for paediatric medicines process has provided a series of relevant recommendations (panel 2).[15] In what follows, we highlight key aspects of study design and conduct that could be improved.

First, lessons could be learned from failed randomised trials. Randomised controlled trials are described as the gold standard for testing efficacy and tolerability of medications, but insufficient recruitment or a failed supply chain of study drugs are a serious threat to their success. Before designing a study, seeking active involvement of people with lived experience in the study design is crucial, in line with the European Clinical Trials Regulation.[16] Once the trial is completed, sharing study results with study participants is mandated by the European Clinical Trials Regulation. Another important aspect is the development of regional research networks to improve recruitment from non-university hospitals or community services, with the support of people with lived experience.

Second, placebo effects need to be understood and minimised in trials. Both increased placebo effects and reduced placebo-subtracted drug effects have been associated with various designs, trial conduct, and participant variables, some of which are interrelated.[17,18] Factors that increase the likelihood of drug–placebo separation should be carefully considered and addressed when designing and conducting clinical trials aiming at regulatory approval. These factors include the following: in general, do not include an open-label lead-in phase before randomisation;[19] use as few study sites, active arms, and study participants as possible;[20] randomly assign more participants to placebo, as this decreases the expectation bias of receiving an active intervention, and after an extended wash-out period[20] (if feasible and ethical depending on the condition); use validated diagnostic and symptom rating instruments; conduct trials of longer than 4 weeks duration in acute settings;[20] and include severely affected participants[21] and those with a first-episode or shorter illness duration (appendix p 12). Although the generalisability of the findings might be somewhat reduced by focusing on populations with specific characteristics, being able to show separation of the active intervention from placebo on the primary outcome is of foremost importance. Notably, evidence supporting these statements derives mainly from adult studies in schizophrenia or depression; there is a clear need to conduct analyses of placebo and nocebo effects in youth with specific disorders. Additionally, the use of centralised researchers might help to identify appropriate participants and reduce placebo effects by reducing expectation bias.[17]

Third, studies should be incentivised to include outcome measures beyond the core symptoms, including outcomes that are relevant for the patients such as patient-reported outcome measures.[22] The EMA now endorses the use of functional and quality of life outcomes in addition to the traditional symptom outcomes. However, there is an urgent need to identify valid and reliable functional outcome measures for children and adolescents with mental health conditions and to agree on the best way to measure them (eg, which domain, instrument, and rater). It is also crucial to gain insight into the relative benefits and weaknesses of patient, caregiver, and clinician ratings of these outcomes in particular age groups and for specific indications. Although the EMA currently recognises cognitive outcomes as a critical component of long-term safety, the inclusion of cognitive outcomes as secondary measures of efficacy, monitoring, and stratification should also be encouraged. However, there are still several barriers to

	Participants (N=644)	
	N	%
What do you think are the most important questions on medicines for children or teenagers with mental problems that researchers should try to answer in the future?		
Rationale for using medications		
When a non-pharmacological intervention is better	24	3·72%
Why a pharmacological treatment is needed	5	0·77%
What are the effects of taking versus not taking medications	1	0·16%
What are the goals of the pharmacological treatment	1	0·16%
Efficacy–effectiveness		
Finding curative rather than symptomatic treatments	15	2·33%
Efficacy versus tolerability	9	1·39%
Efficacy	6	0·93%
Improve adherence	4	0·62%
Tolerance	4	0·62%
Find medications with effectiveness	3	0·47%
Costs–benefits	3	0·47%
Effects on quality of life	3	0·47%
Understand factors that might increase the effects of medications (eg, diet or exercise)	3	0·47%
How to measure if a medication is working	1	0·16%
Improve duration of action	1	0·16%
Timely treatment	1	0·16%
Tackling prodromal symptoms	1	0·16%
Aiming at normalisation	1	0·16%
Risk of not taking medications	1	0·16%
Disorders or conditions for which (additional) medications are needed		
Cognitive issues or executive dysfunctions	2	0·31%
Disorders of early childhood	2	0·31%
Academic underperformance	1	0·16%
Agitation	1	0·16%
Conduct disorders	1	0·16%
Emotional dysregulation	1	0·16%
Inattention	1	0·16%
Sleep disturbance	1	0·16%
Tolerability and safety		
Understanding side effects (in general or in the long-term more specifically)	361	56·05%
Potential of medication of being addictive	83	12·88%
Effects on brain	9	1·39%
Contraindications	8	1·24%
Negative effects on personality	6	0·93%
Rebound effects	4	0·62%
Negative effects on weight	3	0·47%
Interactions among medications	2	0·31%
Negative effects on cognitive functions	2	0·31%
Finding medications with fewer side effects	1	0·16%
Link with neurodegenerative disorders	1	0·16%
Practical issues related to prescribing		
Individualise treatment	10	1·55%
Finding alternative formulations	10	1·55%

(Table 2 continues in next column)

	Participants (N=644)	
	N	%
(Continued from previous column)		
How to adjust the dose	6	0·93%
How long the medication should be taken for	6	0·93%
Assessing long-acting formulations	4	0·62%
How to taper down	3	0·47%
What are second-line medications	1	0·16%
Other		
Stigma	8	1·24%
How to train prescribers	2	0·31%
How to make medications more accessible	2	0·31%
Ethical aspects	1	0·16%
Involve parents in decision making	1	0·16%
Which professionals should prescribe	1	0·16%
Should we treat the child or the society	1	0·16%
In your opinion, do people think that taking medicines for mental problems is bad?		
Yes	518	80·43%
Often	103	15·99%
No	95	14·75%
It depends (on the type of problem, medication, person)	28	4·34%
Sometimes	8	1·24%
I don't know	12	1·86%
Maybe	2	0·37%
What do you think we could do to help people understand that medicines may help children and teenagers with mental problems?		
Education on mental health issues and their treatment	216	33·54%
Education lead by people with personal lived experience	91	14·13%
Finding medications with good efficacy or risk ratio	49	7·60%
Train mental health professionals	39	6·05%
Presenting the mechanism of action of medications in a clear way	32	5·06%
Train school personnel	27	4·96%
Make study results accessible to lay people	22	3·41%
Studies showing effects before and after medication	17	2·63%
Showing efficacy in the short and long term	16	2·48%
Associate the medication to non-pharmacological strategies	16	2·48%
Showing effects on quality of life	15	2·23%
I don't know	15	2·23%
Discussing the effects of not medicating	12	1·86%
Using the model of other medical conditions (we pharmacologically treat epilepsy…why not mental conditions?)	11	1·70%
Fight stigma	10	1·55%
Presenting medication as second-line choice after nonpharmacological options	7	1·08%
Education promoted by adults who used medication in childhood	4	0·62%
Educating via media	4	0·62%
Help accepting the disorder	3	0·47%
Showing medication does not change the personality	3	0·47%

(Table 2 continues in next column)

Health, Zucker Hillside Hospital, New York, NY, USA (Prof C U Correll)**; Department of Psychiatry and Molecular Medicine, Zucker School ofMedicine, Hempstead, NY, USA** (Prof C U Correll)**; Center for Neuroscience, Feinstein Institute for Medical Research, Manhasset, NY, USA** (Prof C U Correll)**; Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital Zurich, University of Zurich, Zurich, Switzerland** (Prof E Grünblatt PhD, Prof S Walitza MD)**; Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland** (Prof E Grünblatt, Prof S Walitza)**; Neuroscience Center Zurich, Swiss Federal Institute of Technology and University of Zurich, Zurich, Switzerland** (Prof E Grünblatt, Prof S Walitza)**; University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry & Accare Child Study Center, Groningen, Netherlands** (Prof P J Hoekstra PhD)**; Department of Psychiatry, Oxford University, and Oxford Health Biomedical Research Centre, Oxford, UK** (A James MD)**; Oxford Health NHS Foundation Trust, Oxford, UK** (A James)**; Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark** (Prof P Jeppesen PhD, Prof A K Pagsberg PhD)**; Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, Copenhagen, Denmark** (Prof P Jeppesen)**; Bethesda Children's Hospital, Budapest, Hungary** (P Nagy MD)**; Child and Adolescent Mental Health Center, Copenhagen University Hospital – Mental Health Services CPH, Copenhagen, Denmark** (Prof A K Pagsberg)**; Child & Adolescent Neuropsychiatry, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy** (Prof A M Persico MD)**; Department of Child and Adolescent Psychiatry and Psychotherapy, Faculty of Medicine, Technische Universität Dresden, Dresden,**

Germany (Prof V Roessner MD); **Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK** (Prof P Santosh PhD, Prof E Simonoff MD); **Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD),** (Prof P Santosh), **South London and Maudsley NHS Foundation Trust (SLaM), London, UK** (Prof E Simonoff); **Maudsley Biomedical Research Centre for Mental Health, London, UK** (Prof E Simonoff); **Clinic for Neurology and Psychiatry for Children and Youth, Belgrade, Serbia** (D Stevanovic PhD); **Gillberg Neuropsychiatry Centre, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden** (D Stevanovic); **Department of Clinical, Educational and Health Psychology, Division of Psychiatry** (Prof A Stringaris PhD), **and Research Department of Practice and Policy, School of Pharmacy** (Prof I C K Wong PhD), **University College London, London, UK; Department of Psychiatry, National and Kapodistrian University of Athens, Athens, Greece** (Prof A Stringaris); **Division of Child and Adolescent Neuropsychiatry, Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy** (Prof B Vitiello MD); **Geha Mental Health Center, Petah Tikva, and Department of Psychiatry, Faculty of Medicine, and Laboratory of Biological and Molecular Psychiatry, Felsenstein Medical Research Center, Tel Aviv University, Tel Aviv, Israel** (Prof A Weizman MD, Prof G Zalsman MD); **Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong Special Administrative Region, China** (Prof I C K Wong); **Laboratory of Data Discovery for Health (D24H), Hong Kong Science Park, Hong Kong Special Administrative Region, China** (Prof I C K Wong); **Aston Pharmacy School, Aston University, Birmingham, UK** (Prof I C K Wong); **Division of**

	Participants (N=644)	
	N	%
(Continued from previous column)		
Saying that medication is only a temporary help	3	0·47%
Trial of medication with strict monitoring	21	0·33%
Education promoted by famous people with the disorder	21	0·33%
Publish more studies	21	0·33%
Education to children in school	21	0·33%
Improve ethical procedures of drug companies	1	0·16%
Urge caution vis-à-vis what is reported by lay press	1	0·16%
Promote empathy for people who need medication	1	0·16%
Studies not funded by drug companies	1	0·16%
Education especially for newer medications	1	0·16%
Doing studies on natural products	1	0·16%
Use simple examples (eg, like wearing glasses)	1	0·16%
Normalise the concept of mental condition	1	0·16%
Make service access easier	1	0·16%
Seeing medication as the last resort	1	0·16%
Trusting professionals rather than internet	1	0·16%
Listening to parents' concerns and discuss with them	1	0·16%
Patience and persistence	1	0·16%
Consider faith or religion of parents	1	0·16%
Education independent from drug companies	1	0·16%

Table 2: **Results of the survey among experts by lived experience**

Panel 2: Recommendations from the European Network of Paediatric Research at the European Medicines Agency Working Group on preparedness of clinical trials about paediatric medicines process[35]

- Start early, preferably while designing the medicine's development plan and individual protocols, and identify the rationale and clinical need
- Listen to the perspectives of people with lived experience
- Determine how many participants will be eligible for the trial
- Calculate the resources needed
- Use all available data to estimate feasibility
- Present information about preparedness in a structured way
- Deploy appropriate resources to support the preparation of trials

the effective use of cognitive measures in clinical trials. There is a need to generate developmentally sensitive norms similar to those for growth and blood pressure. Notably, guidance for major depressive disorder is currently under revision by the EMA, and cognitive deficit as a separate domain in depression has been suggested as a topic for discussion.[23]

Fourth, developmental windows should be considered. When researching medication effects on children and adolescents, it is essential not only to focus on the optimal compound and dose, but also to consider whether age could affect response to medication or study design. Adapting the timing of interventions to the underlying developmental windows and considering pubertal maturation stages could be particularly relevant for neurodevelopmental conditions. The effects of medications on normative development, and the differential adverse event profiles across development, should also be studied.

Fifth, trials comparing pharmacological and non-pharmacological interventions are useful. Understanding when pharmacological treatments or non-pharmacological approaches would be the most appropriate option, or when both options should be offered, is a key need and priority that was highlighted by people with lived experience in our survey. Although rigorously comparing these two types of interventions is challenging from a methodological standpoint, the use of placebo-control and sham groups in the same study[24] should be further encouraged in the field to address these important questions.

Sixth, studies should move beyond standard placebo-controlled trials. Randomised controlled trials are not well suited to studying patients representative of those in mental health services, rare adverse events, long-term effectiveness, and other real-world outcomes. Pharmacoepidemiological studies using large datasets are an alternative option to evaluate these outcomes.[25] Their key strength is their potential for large sample sizes and to detect rare adverse outcomes.[26] Several self-controlled methods have been developed, such as within-individual case series, where comparisons are made within the same participant during times that they are on and off medication to evaluate the safety of pharmacotherapy, mainly in the field of ADHD treatments.[27–29] This type of study design has advantages over classic cohort and case-control designs as it effectively controls the effects of time-invariant confounders and it substantially reduces confounding by indication.[30] Another methodological advancement in observational studies is the so-called emulated trial,[31,32] which refers to applying design principles from randomised trials to the analysis of observational data.[33] Emulated trials are valuable in paediatric psychopharmacology because very few comparative clinical trials are available or feasible. Placebo-controlled discontinuation designs, in which individuals treated with active medication are randomly assigned to continue the active medication or to placebo, are the preferred method to study (ongoing) long-term effectiveness,[34] and use of this trial design should be encouraged, alongside naturalistic, longitudinal controlled studies,[35] to assess safety outcomes, including the potential of addiction. As data from spontaneous reporting systems (eg, EudraVigilance)[36] are limited, research on these systems should be encouraged. Stepped wedge cluster randomised trials, platform trials, and in silico trials might also offer unprecedented opportunities (for definitions see appendix p 13). Randomised designs embedded in decentralised clinical

trials that are based in routine care allow continuous learning evaluation and are essential to the strategic improvement of health care.[37]

Seventh, clinical and research interest has moved away from a one-size-fits-all approach in clinical care towards precision medicine approaches, which aim to support clinical recommendations and decisions for well defined groups sharing similar clinical characteristics or profiles of biomarkers. Implementing these approaches implies that biomarkers have been identified and clinically validated, but stratification markers have not been validated for any paediatric psychiatric disorders. Notably, pharmaceutical companies have generally not incorporated candidate biomarkers in registration studies, and there has been a paucity of funding opportunities for academically initiated clinical trials or observational studies of biomarkers. As suggested by a large-scale systematic review,[38] although it is unlikely that a focus on a single biomarker could lead to successful discovery, future multivariable and multi-level biomarker approaches could be best suited to finding valid candidate stratification biomarkers, overcoming the replication crisis in the field.[39] Those biomarkers would then need to be validated in independent samples, and their feasibility and cost-effectiveness would need to be tested in cost-effectiveness pragmatic trials before biomarkers could be implemented in clinical practice.

Therapeutic drug monitoring can guide clinical decision-making regarding compliance, dose calibration, and drug–drug interactions. Combining therapeutic drug monitoring with other methods, such as pharmacogenetics, could facilitate a personalised medicine approach. For example, a flexible-dose study[40] in therapeutic drug monitoring showed a statistically significant diagnosis-specific relationship between sertraline serum concentration and clinical efficacy for paediatric obsessive compulsive disorder. The evolution of wearable electrochemical sensors has led to promising developments for on-body analyses.[41] Future investigations should assess the feasibility and practicalities of using such devices in children. Linking therapeutic drug monitoring with pharmacogenetics and epigenetic studies could be a successful avenue.

Investigation, research, and implementation of digital technologies

Digital technology integration ranges from incorporating artificial intelligence in diagnostic devices to using real-world data (eg, electronic health records) for study recruitment or as pharmacovigilance platforms to improve drug therapy safety. In some cases, clinical trials can now be conducted virtually, potentially reducing the need for in-person interaction.[42]

Secure digital platforms can assist in conducting remote, decentralised clinical trials, and digital solutions might help to improve efficiency and flexibility and make participation more inclusive in clinical trials. Although challenges remain, progress is encouraging, and careful planning and patient and family involvement in study design can overcome barriers. It is crucial to gain insight into the extent to which digital tools are acceptable and safe for children and adolescents (eg, autistic children might find some wearable devices uncomfortable), and which clinical conditions could benefit the most from these technological advances.

Ecological momentary assessment could address the issues related to the use of retrospective self-reports through electronic patient-reported outcome measures collected at research or clinic visits, which are limited by recall bias. Ecological momentary assessment[43] involves the repeated sampling of patients' current behaviours and experiences in real-time, in natural environments. In addition to minimising recall bias, it can maximise ecological validity, and allow the study of microprocesses that influence behaviour in real-world contexts. This approach can assess events in patients' lives or assess issues at periodic intervals, often by random time sampling, using technologies ranging from written diaries and telephones to electronic diaries and physiological sensors that track dynamic behavioural and physiological patterns. Ecological momentary assessment could be used in disorders and symptoms such as hyperactivity, emotional dysregulation, depression, anxiety, and bipolar disorder, and it could allow the development of transdiagnostic approaches by integrating categorical and dimensional assessments.[44]

Focusing on individuals whose symptoms have not responded to initial treatment

Individuals with treatment-resistant conditions (usually defined as no substantial improvement in symptoms after exposure to two adequately dosed therapeutic drugs[45]) are often excluded from trials.[46] As a consequence, evidence-based practice in paediatric psychopharmacology ends when symptoms do not respond to initial treatment, leaving clinicians to make treatment decisions based on a lower level of evidence, and frequently leading to trial-and-error polypharmacy in clinical practice. Therefore, trials should be encouraged to include people with treatment-resistant conditions, focusing on augmentation strategies and the possible adjuvant role of non-pharmacological approaches such as psychotherapy, inpatient care, and dietary interventions.

The need for innovations in regulatory and legislative frameworks

Small market share and pharmaceutical and ethical challenges have hindered developing a substantive evidence base to inform the use of psychopharmacological treatments, including appropriate doses, in children and young people.

The 2017 European Commission Ten Year Report on the implementation of the Paediatric Regulation[47] indicated a global increase in trials and authorised

Molecular Imaging and Neuropathology, Department of Psychiatry, Columbia University, New York, NY, USA (Prof G Zalsman); **Department Biomedical Science, Sect Neuroscience & Clinical Pharmacology, University of Cagliari, A. Cao Paediatric Hospital, Cagliari, Italy** (Prof A Zuddas MD*, S Carucci PhD); **European Medicines Agency, Human Medicines Division, Amsterdam, Netherlands** (F Butlen-Ducuing PhD, M Tome PhD); **ADHD Germany, Berlin, Germany** (M Bea); **Hypersupers TDAH France, National Association, Paris, France** (C Getin BSc); **ADHD Europe, Brussels, Belgium** (N Hovén MSc); **Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden** (A Konradsson-Geuken PhD); **European Federation of Associations of Families of People with Mental Illness (EUFAMI), Leuven, Belgium** (A Konradsson-Geuken PhD); **Global Alliance of Mental Illness Advocacy Networks- Europe (GAMIAN Europe), Ixelles, Belgium** (D Lamirell, N Olisa); **Patient Engagement in Research Department, Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain** (B Nafria Escalera PhD); **Innovation Department Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain** (B Nafria Escalera)

*Prof A Zuddas died in July, 2022

Correspondence to:
Prof Samuele Cortese, Centre for Innovation in Mental Health (CIMH), Faculty of Environmental and Life Sciences, University of Southampton, Southampton SO17 1BJ, UK
samuele.cortese@soton.ac.uk

See **Online** for appendix

medicines for children in different therapeutic areas over the previous 10 years. However, psychiatry accounted for only 2·4% of the therapeutic areas across medicine. The development of a paediatric investigation plan (appendix p 5) is a requirement for marketing authorisation for new medicines or indications of an already authorised medicine covered by intellectual property rights, unless a deferral or waiver is provided. However, even though the regulation provided funding to support off-patent medications through EU Framework Programme 7, only three paediatric-use marketing authorisation applications were granted.

The EMA developed an action plan to improve the implementation of regulations and structured guidance for extrapolating data from adults to young patients,[48] including the following: identifying paediatric medical needs; strengthening cooperation between decision makers; ensuring timely completion of paediatric investigation plans; improving the handling of paediatric investigation plan applications; and increasing transparency around paediatric medicines. This action plan highlights the advantages of early submission and timely completion of a paediatric investigation plan, which could facilitate global developments. An assessment of the appropriateness of paediatric studies showed that 66% of the studies were needed for confirming the safety and efficacy of treatments in a paediatric population, 22% could have been done more appropriately if all relevant data had been used to develop a well designed extrapolation study, and 12% of studies were considered unnecessary.[49] Extrapolation can be based on similarities between the source and the target population regarding physiology, maturation, pharmacokinetics, and pharmacodynamics. Extrapolation can offer a rationale for including adolescents in adult trials in some medicine developments. Physiologically based pharmacokinetics and simulation might also be promising tools for paediatric trials.[50]

For the **Innovative Health Initiative programme** see https://www.ihi.europa.eu/

The standards used by regulators to determine efficacy and safety have risen substantially in recent years. Although this development is positive, it does give rise to the question of whether there should be procedures to review the approvals and summaries of product characteristics for medications that were licensed before the standards were raised. For this to happen, there would need to be adequate opportunity to address the current gaps in the evidence with new studies, which would require public funding as it is unlikely that pharmaceutical companies would be willing to pay for expensive new studies of generic medications. The authors believe that such an investment, particularly in large-scale pharmacovigilance studies with the potential to reduce the risk of harm, is justified and should be a priority for research funders. The EMA encourages repurposing authorised medicines for new indications in cases where marketing authorisation holders are unlikely to undertake the research and regulatory steps needed.[51]

A key consideration relates to the possibility of including adolescents in randomised controlled trials recruiting adults.[52] Alternative options include encouraging the development of parallel trials (in adults and adolescents or children) in conditions with high unmet needs at young ages, after pharmacokinetic studies in adolescents and after gathering some safety data, to speed up the availability of medications for young populations. Another alternative option is to encourage the development of trials accounting for the clinical specificities of paediatric conditions when strong neurobiological underpinnings have been proven (eg, targeting irritability across paediatric conditions). The appendix (p 5) summarises critical regulatory and legislative initiatives for facilitating paediatric drug development.

Innovation in the way research is conducted, reported, and promoted

Compared with other areas of medicine, brain research has been traditionally underfunded, particularly in children and adolescents, at both national and European levels, despite being prioritised by different stakeholders.[53,54] EU funding was successfully obtained over the past 10 years for several projects (eg, PERS,[55] ADDUCE,[35] TACTICS,[56] Aggressotype,[57] MATRICS,[57] EU-AIMS,[58] and AIMS-2-TRIALS[59]) to deepen understanding of the biological and genetic mechanisms and management of paediatric aggression, ADHD, autism, and compulsivity disorders. The funding did not, however, allow progress to be made in testing new pharmacological interventions within these projects, except for the Innovative Medicines Initiative-supported AIMS-2-TRIALS project, which is based on a collaboration between academia and pharmaceutical companies.[60] A more systematic, collaborative approach between academia and companies would benefit other paediatric psychiatric disorders within the framework of the Innovative Health Initiative programme, which is the successor of the Innovative Medicines Initiative programme. There is also a need to have stable EU funding for networks of centres of excellence. Even though some countries have their own mental health networks,[61,62] an umbrella network or specific topics among those networks would be beneficial for future research. Collaboration among centres in different European countries, as has been the case for the past 15 years with the ECNP–C&A, would allow for large cohorts of patients in naturalistic and pragmatic studies with harmonised assessment and outcomes (including patient-reported outcome measures and patient-reported experience measures). Enhanced collaboration is needed not only for testing new medications, but also for addressing another key issue, the low accessibility to evidence-based treatments, as, for instance, no more than one third of those with moderate-to-severe mental disorders in the UK were in specialist or non-specialist treatment.[63] Decisions on research priorities should be

more participatory (eg, involve people with lived experience) to increase the acceptability of results among the population and therefore their economic value.

Evidence synthesis of data from individual studies is paramount for informing future clinical guidelines. Aggregate-level meta-analyses give averages of data across groups of participants and are the usual method in mental health. Individual-patient data meta-analyses, especially when coupled with data from observational studies,[64] have the potential to inform treatment modifiers within the framework of a precision psychiatry approach, and should therefore be encouraged.

Network meta-analyses allow the comparison of two or more treatments even when they have not been directly compared in the trials within the meta-analysis. Although network meta-analyses have become more frequent in child and adolescent mental health research,[65] most of them have focused on pharmacological or non-pharmacological treatments separately. However, under some methodological assumptions, it is possible to compare pharmacological and non-pharmacological treatments in the same network.[66] Therefore, this approach could help provide evidence informing the comparison of pharmacological versus non-pharmacological treatments.

When referring to psychotropic medications, prescribers usually use terms such as antidepressants or stimulants, which can be confusing in cases when, for example, an antidepressant is used to treat anxiety or a stimulant is recommended for an overactive child. To address this issue, the Neuroscience based Nomenclature (NbN) was developed in 2009 to provide an approach to psychotropics classification based on a medication's putative mechanisms of action. The NbN Child and Adolescent was released in 2018.[67] Although the NbN Child and Adolescent is still a work in progress, it should stimulate the implementation of a nomenclature that is less confusing.

As highlighted by our survey among experts by lived experience, education and training delivered by people with lived experience are crucial to reducing stigma, not only to children and their caregivers, but also to school personnel. Referring to disease models, such as epilepsy, where the use of psychotropic medications is better accepted, can be helpful in fighting stigma against people with mental illness and the use of psychotropic medications for mental health conditions.

Conclusions

There are substantial challenges and important opportunities in child and adolescent psychopharmacology, which should be addressed by a joint effort among patients, their families, clinicians, scientists, funders, and regulators. Key opportunities include learning from failed trials, reducing the placebo effect in trials, assessing outcomes beyond core symptoms, considering developmental stage, comparing pharmacological and non-pharmacological treatments, using innovative designs beyond standard randomised controlled trials, moving towards precision medicine and stratification approaches, investigation and implementation of digital technologies, focusing on conditions that are non-responsive to initial treatment, improving the regulatory and legislative framework, and innovation in the way research is conducted, reported, and promoted.

Contributors

SC and CM conceived the idea. All the authors contributed to the structure, drafting, and critical editing of the paper. All authors approved the final version of the paper.

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