Psychopharmacology in children and adolescents: unmet needs and opportunities

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SUMMARY

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 conditions in children and adolescents. Here, we present the first position paper to highlight and address unmet needs and opportunities in the field, including the perspective of clinicians/researchers from the European College of Neuropsychopharmacology-Child & Adolescent Network (ECNP-C&A), alongside that of experts by lived experience from national/international associations - via a survey involving 644 participants from 13 countries - and regulators, through representation from the European Medicines Agency (EMA). We present and discuss the evidence base for medications currently used for mental disorders in children and adolescents, medications in the pipeline, the opportunities in the development of novel medications, critical priorities for the conduct of future clinical studies, challenges, as well as 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 (e.g., neurodevelopmental disorders) peaking in childhood and 'later onset' disorders peaking in adolescence and young adulthood, with onset before the age of 18 in around 50% of the cases.[1] Therefore, preventive/treatment strategies in childhood/adolescence are crucial to decrease the burden of mental illness. Pharmacotherapy is a key component in the multimodal strategy for managing mental conditions in children/adolescents.

Overall, international pharmacoepidemiological data point to increased use of psychotropic medications for children/adolescents in past two decades. In a study across 65 countries, the total psychotropic medications sales in children and adults increased from 2008 to 2019, with a relatively average annual increase of 4·08% (95% CI 2·96-5·21).[2] Likewise, other international studies have shown increasing trends of specific psychotropics use in children/adolescents, including ADHD medications [3] and antidepressants.[4]

However, high unmet needs and opportunities remain, alongside possible risks to consider. In particular, relatively few medications are licensed for children/adolescents, with most drugs still being tested first in adults. This limits and/ delays access to medications for children/adolescents. Additionally, there is limited evidence about the developmental impact of psychotropics. Furthermore, while increases in the consumption of psychotropics by children/adolescents may relate to a perceived increase in need, it may also be accounted for by poor or variable access to other treatments (i.e., evidence-based psychotherapy), which may be as or more effective for some conditions. Lastly, medications may 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 (ECNP)-Child & Adolescent Network (ECNP-C&A) on unmet needs in child/adolescent

psychopharmacology, this international position paper is the first to address unmet needs and opportunities in the field, that includes not only the perspectives of clinicians/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 Europe.

CURRENT SITUATION

Psychotropic medications currently used for mental conditions in children and adolescents

Psychopharmacological medications approved – as of June 2023- by the European Medicine Agency (EMA) in Europe, and, by comparison, the Food and Drug Administration (FDA) in the USA, for mental conditions in children/adolescents, are reported in table 1. This reflects only a small portion of medications approved for mental health conditions in children/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 though not approved centrally and can take actions, if necessary, on those. Supplemental Table 1 lists psychotropics currently unlicensed in Europe or by the FDA but identified by our network as commonly used off-label (i.e., outside the limits of the marketing authorization or product license[6]). Often, but not always (e.g., most medications for ADHD), medications for mental conditions are first approved in adults, and then manufacturers can apply for an extension in children/adolescents based on the provision of

sufficiently strong evidence from clinical trials and/or on extrapolation concepts in line with the obligatory paediatric development plan agreed with EMA or FDA. Supplemental table 2 lists antipsychotics and antidepressants approved in adults via the EMA centralised procedure (a procedure for the authorisation of medicines, with is a single application, a single evaluation, and a single authorisation throughout the European Union) and the outcomes of applications for extensions to children/adolescents from 1995 to 2022. Guidelines for the EMA extension of license and extrapolation are reported in Appendix 2.

The evidence base for currently used psychotropic medications

Over the past decades, an increasing body of evidence has been generated from randomised controlled trials (RCTs) and observational studies assessing the efficacy/effectiveness, and tolerability/safety of medications for specific disorders in child/adolescent mental health. An umbrella review, found the highest effect sizes in relation to efficacy[7] for: stimulant for core symptoms of ADHD; aripiprazole and risperidone for irritability in autism spectrum disorder (ASD); 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; fluoxetine/other selective serotonin reuptake inhibitors (SSRIs) for obsessive compulsive disorder (OCD); and imipramine for enuresis.

Another umbrella review on tolerability/safety[8] found the best tolerability/safety profile for escitalopram and fluoxetine, lurasidone, methylphenidate, and lithium. The most common adverse events were: nausea/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 stabilizers.

Unmet needs

With the available body of evidence, critical unmet needs are evident. There are disorders for which no evidence-based or no well-studied pharmacological interventions are available. A survey among the members of the ECNP-C&A network on the disorders/conditions for which there is a need for additional pharmacological development identified the following, listed in order based on the number of votes: 1) autism spectrum disorder (core symptoms); 2) emotional dysregulation/irritability; 3 and 4) with an equal score: anorexia nervosa and depression ; 5) suicidal behaviours; 6) conduct disorder/aggressiveness; 7) addiction to drugs/alcohol; 8) with equal score: negative symptoms of schizophrenia and insomnia/sleep disorders; 9) anxiety; 10) rare diseases, such as Prader Willi syndrome; 11-17) and, with an equal score: borderline personality disorder, eating disorders other than anorexia nervosa, OCD, body dysmorphic disorder, cognitive dysfunction in intellectual disability, somatoform symptoms, and ADHD comorbid with cocaine or methamphetamine addiction.

Moreover, the members of the ECNP C&A network identified other critical unmet needs related to scarcity of evidence, including: 1) most compounds are tested in single trials vs placebo; there is a need for additional trials a) directly comparing two or more active medications and b) for children/young people who do not respond or c) cannot tolerate the first options; 2) in contrast to the current tendency to focus on a few core symptoms, the impact of medications on other important outcomes (e.g., functional outcomes) should be explored; and 3) our 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) highlighted additional specific unmet needs from their perspective. Responses, summarised in table 2, pointed to knowledge on safety and tolerability – including the potential of medications of being addictive- as the main unmet needs, alongside a need for a

clear understanding on comparative effects of pharmacological and non-pharmacological interventions.

HOW TO ADDRESS THE CURRENT NEEDS- OPPORTUNITIES IN THE FIELD

Medications in the pipeline

A systematic review[9] explored RCTs in phases 2, 3, and 4 of novel medications, or medications used for unlicensed indications ("off-label"), for child/adolescent mental conditions, alongside RCTs of dietary interventions/probiotics as well as phase 4 RCTs of agents targeting unlicensed indications for children/adolescents with mental health disorders. The review retrieved 234 ongoing or completed RCTs, including 26 (11%) with positive findings on ≥ 1 primary outcome, 43 (18%) with negative/unavailable results on every primary outcome, and 165 (70%) without publicly available statistical results. The only two compounds with evidence of significant effects that were replicated in at least two RCTs without any negative RCTs were dasotraline for ADHD (whose developmental program, however, was halted by the manufacturer in 2020) and carbetocin for hyperphagia in Prader-Willi syndrome. However, there are still opportunities for the development of novel molecules and/or with a different mechanism of action. For instance, S-enantiomer of racemic ketamine, esketamine, got central approval in 2019 for treatment resistant depression and then the indication was extended to rapid reduction of depressive symptoms in 2021.[10,11] While pre-clinical animal studies are a major bottle neck 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 address these challenges, while reducing the number of animals used.[13] Cell reprogramming has opened the possibility to generate personalized patient-specific induced pluripotent stem cells (iPSC) from

peripheral somatic cells (e.g., blood), preserving their genetic background.[13] The use of an *in vitro* high-throughput screening (HTS) platform has demonstrated the potential of iPSCs as a drug screening platform. For instance, for fragile X syndrome, a proof of principle using FMR1-luciferase reporter iPSC lines HTS and cell viability screening demonstrated the utility of human cell-based methods to detect reactivators of the FMR1 gene.[14]

Opportunities for future clinical studies

The conduct of clinical trials in children and young people may be hampered by issues that could have been anticipated. The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) Working Group on preparedness of clinical trials for paediatric medicines process has provided a series of relevant recommendations[15] (see Panel 2).

In the following subsections, we highlight key aspects in terms of improvement of study design and conduct.

Lessons learned from failed RCTs

RCTs are the gold standard for testing efficacy and tolerability of medications. However, insufficient recruitment or failed supply chain of study drugs are a serious threat to the success of an RCT 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 around the development of regional research networks able to improve recruitment from non-university hospitals or community services, with the support of people with lived experience.

Understanding and minimising the placebo effects

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 include: 1) in general, not including an open-label lead-in phase prior to randomization;[19] 2) use fewer study sites, active arms, and study participants,[20] 3) randomize more participants to placebo and after a more extended wash-out period,[20] (if this is feasible and ethical depending on the condition); 4) utilize validated diagnostic and symptom rating instruments, 5) conduct trials of longer duration, [20] 6) include more severely affected participants,[21] and those with a first-episode or shorter illness duration (Supplemental table 3). Notably, evidence supporting these statements derives mainly from adults studies in schizophrenia or depression, there is still a clear need to conduct analyses of placebo/nocebo effects in youth with specific disorders. Additionally, the use of centralized researchers may help identify appropriate patients and reduce placebo effects by reducing expectation bias.[17]

Assessing outcomes beyond core symptoms

Studies should be incentivised to include outcome measures beyond core symptoms, relevant for the patients, including patient reported outcome measures (PROMs).[22] The EMA now endorses the use of functional and quality of life outcomes in addition to the traditional symptom outcomes. However, we urgently need to identify valid and reliable functional outcome measures for this population of children/adolescents with psychiatric disorders and agree on the best way to measure them (e.g., which domain, instrument, and rater). It is also crucial to gain insight into relative benefits and weaknesses of patient', caregiver' and

clinician's ratings of these outcomes in particular age groups and for specific indications. While the EMA currently recognises cognitive outcomes as a critical component of long-term safety, their inclusion as secondary measures of efficacy, monitoring, and stratification should also be encouraged. However, there are still several barriers to the effective use of cognitive measures in clinical trials. We need to generate developmentally sensitive norms similar to those we have 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 flagged as a topic for discussion.[23]

Consideration of developmental windows

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 may have impact on response to medication as well as on study design. Adapting the timing of interventions to the underlying critical developmental windows, considering pubertal maturation stages, may be particularly relevant for neurodevelopmental conditions. The effects of medications on normative development, and the differential event adverse profiles across development, should also be a matter of exploration.

Trials comparing pharmacological and non-pharmacological interventions

Understanding when pharmacological treatments are appropriate and when, by contrast, 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. While rigorously comparing these two types of interventions has been challenging from a methodological standpoint, the use of placebo-control and sham arms in the same study (e.g.,[24]) should be further encouraged in the field to address these important questions.

Moving beyond standard placebo-controlled randomised trials

RCTs are not well suited to study real-word patients, rare adverse events, long-term effectiveness, and other real-world outcomes. Pharmacoepidemiologic studies using large datasets are currently 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] In recent years, several self-controlled methods have been developed, such as within-individual case series - make comparisons within the same subject during times that they are on and off medication- to evaluate the safety of pharmacotherapy, mainly in the field of ADHD treatments.[27,28] [29] They have advantages over classical cohort and case-control designs as they effectively control the effects of time-invariant confounders and significantly reduce 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 randomized trials to the analysis of observational data, thus explicitly tying the analysis to the trial that is emulating.[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 randomised to continue the active medication or to placebo, are the preferred method to study (ongoing) long-term effectiveness,[34] and their

use should be encouraged, alongside naturalistic, longitudinal, controlled studies (e.g.,[35]) to assess safety outcomes, including potential of addiction. As data from spontaneous reporting systems (e.g., EudraVigilance)[36] are limited, research on these systems should be encouraged further.

Additionally, stepped wedge cluster randomized trials, platform trials, and in silico trials, may offer unprecedented opportunities (see Supplemental table 4 for definitions of these trials). Finally, randomized designs embedded in routine care-based-decentralised clinical trials (DCTs) allow continuous learning evaluation and are essential to the strategic improvement of healthcare.[37]

Moving towards precision medicine/stratification approaches

Biomarkers

Clinical and research interest has moved away from a 'one-size-fits-all' approach of clinical care towards precision/personalised medicine approaches, which aim to support clinical recommendations and decisions for well-defined groups sharing similar profiles of biomarkers. Implementing these approaches implies the presence of biomarkers that have been identified and clinically validated. However, stratification markers have not been validated for any of the (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], while it is unlikely that a focus on a single biomarker could lead to successful discovery, future multivariable and multi-level biomarker approaches may be best suited to find valid candidate stratification biomarkers, overcoming the replication crisis in the field.[39] It will be

crucial for these to then be validated in external, independent samples, and their feasibility and cost-effectiveness to be tested in cost-effectiveness pragmatic trials before biomarkers can be implemented in clinical practice.

Therapeutic drug monitoring (TDM)

TDM can guide clinical decision-making regarding compliance, dose calibration, and drug–drug interactions. Combining TDM with other methods, such as pharmacogenetics, may facilitate a personalized medicine approach. For example, a TDM–flexible-dose study revealed a significant diagnosis-specific effect between sertraline serum concentration and clinical efficacy for paediatric OCD.[40] 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 TDM with pharmacogenetics and epigenetic studies could represent a fruitful avenue.

Investigation/research/ and implementation of digital technologies

Digital technology integration ranges from incorporating artificial intelligence in diagnostic devices to using real-world data (e.g., 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 decentralized clinical trials. Digital solutions may help improve efficiency and flexibility and make participation more inclusive in clinical trials. While 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 by children and adolescents (e.g., children with autism may find some

wearable devices uncomfortable), and also which clinical conditions may benefit the most from these technological advances.

Ecological momentary assessment

Retrospective self-reports through electronic patient-reported outcome measures collected at research or clinic visits are limited by recall bias. Ecological momentary assessment[43] involves the repeated sampling of subjects' current behaviours and experiences in real-time, in natural environments. It aims to minimize recall bias, maximize ecological validity, and allow the study of micro-processes that influence behaviour in real-world contexts. This approach assesses events in subjects' 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 may allow tracking dynamic behavioural, and physiological patterns. This may have a role in disorders/symptoms such as hyperactivity, emotional dysregulation, depression, anxiety, and bipolar disorder and allow development a transdiagnostic approaches by integrating categorical and dimensional assessments.[44]

Focusing on individuals who have not responded to initial treatment

Individuals with treatment-resistant conditions (usually defined as lack of improvement after exposure to two adequately dosed therapeutic agents[45]) are often excluded from trials.[46] As a consequence, evidence-based practice in paediatric psychopharmacology rapidly ends in case of non-response to initial treatment, leaving clinicians to make treatment decisions based on the lower level of evidence and frequently leading in clinical practice to “trial-and-error” polypharmacy. Therefore, trials should be encouraged in treatment-resistant individuals, focusing on augmentation strategies and the possible adjuvant role of non-pharmacological approaches such as psychotherapy, inpatient care, and diet interventions.

Need for innovations in regulatory and legislative framework

Small market share and pharmaceutical and ethical challenges have represented challenges to building a substantive evidence base that could specifically inform on the use of psychopharmacological treatments, including appropriate dosages, 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 authorized medicines for children in different therapeutic areas over the previous ten years. However, psychiatry accounted for only 2·4% of the therapeutic areas across medicine. The development of a paediatric investigation plan (PIP) (see Appendix 3) 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. Moreover, even though the regulation provided funding to support off-patent medications through EU Framework Programme 7, there were only three granted pediatric-use marketing authorization (PUMA) applications (Appendix 3).

The EMA developed an action plan to improve the implementation of the regulation and structured guidance for the use of extrapolation and from data in adults to young patients,[48] that could hamper paediatric developments including: 1) identifying paediatric medical needs; 2) strengthening cooperation between decision-makers; 3) ensuring timely completion of pediatric investigation plans (PIPs); 4) improving the handling of PIP applications, and 5) increasing transparency around paediatric medicines.

This action plan highlights the advantages of early submission and timely completion of a PIP that may facilitate global developments. An assessment of the appropriateness of paediatric studies showed that 66% of the studies were required, 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. It can offer a rationale for including adolescents in adult trials in some medicine developments. Physiologically based pharmacokinetics (PBPK) and simulation may also be promising tools for pediatric trials.[50]

The standards used by regulators to determine efficacy and, perhaps most importantly, safety have risen substantially in recent years. While this is positive, it does beg the question of whether there should be procedures to review the approvals and summaries of product characteristics for medications licensed before the standards were raised. However, for this to happen, there would need to be adequate opportunity to address the current gaps in the evidence with new studies. This would require public funding as it is unlikely that pharmaceutical companies would be willing to pay for expensive new studies of generic medications. We, however, 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. Repurposing of authorised medicines for new indications in cases where marketing authorisation holders are unlikely to undertake the research and regulatory steps needed is encouraged by EMA.[51]

A specific aspect relates to the possibility of including adolescents in RCTs recruiting in adults.[52] Alternative options include: 1) encouraging development of parallel trials (adults and adolescents/children) in conditions with high unmet needs at young ages, after pharmacokinetic studies in adolescents and after having some safety data, to speed up availability of medications in these populations; 2) encouraging the development of trials accounting for clinical specificities of paediatric conditions when strong neurobiological underpinnings are proven (i.e., targeting irritability across paediatric conditions). Panel 6

summarizes critical regulatory/legislative initiatives for facilitating paediatric drug development.

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

Collaborative efforts and study funding

Compared to other areas of medicine brain research, particularly in children/adolescents, has been traditionally underfunded – at both national and European levels -, despite being prioritized as strategic by different stakeholders.[53,54] EU funding was successfully obtained over the past ten years for several projects (e.g., PERS[55], ADDUCE[35] , TACTICS[56], Aggressotype,[57] MATRICS, EU-AIMS[58] and AIMS-2-TRIALS[59]) to deepen our understanding of the biological/genetic mechanisms and management of paediatric aggression, ADHD, autism, and compulsivity disorders. Funding, however, did not allow progress to be made in testing (new) pharmacological interventions within these projects, except for the Innovative Medicines Initiative (IMI) 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 very much benefit other paediatric psychiatric disorders, within the framework of the new Innovative Health Initiative (IHI) program (https://www.ihi.europa.eu/), the successor the IMI 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 (e.g., [61,62]), an umbrella network of those networks or specific topics among those networks would be desirable for future research. Collaboration among centres in different European countries as it has been the case for the last fifteen years with the ECNP child and adolescent network, would allow for large cohorts of patients in naturalistic and pragmatic studies with harmonized assessment and outcomes (including Patient-Reported Outcome Measures –

PROMs and Patient-Reported Experience Measures- PREMs). Enhanced collaboration is not only needed for testing (new) medications but also to address another critical issue, that is the low accessibility to evidence-based treatments, as no more than one third of those with moderately to severe mental disorders were in specialist or non-specialist treatment.[63] Decisions on research priorities should be more participatory (i.e., involve people with lived experience), increasing acceptability of results among the population and therefore its economic value.

Innovations in evidence synthesis

Evidence synthesis of data from individual studies is paramount to inform future clinical guidelines. Whilst aggregate-level meta-analyses, averaging data across groups of participants, are usually conducted in the field, individual-patient data (IPD) (network)meta-analyses, especially when coupled with data from observational studies,[64] have the potential to inform on treatment modifiers, within the framework of a precision psychiatry approach, and should therefore be encouraged.

Network meta-analyses (NMA) allow to compare two or more treatments even when these have not been directly compared in the trials included in the meta-analysis. While NMAs has gained traction in child and adolescent mental health,[65] most of them have focused on pharmacological or non-pharmacological treatments separately. However, under certain methodological assumptions, it is possible to compare in the same network pharmacological and non-pharmacological treatments.[66] Therefore, this approach may be helpful to provide evidence informing the issue of pharmacological vs non-pharmacological.

Recommendation for protocols and study reporting

When referring to psychotropic medications, prescribers usually use terms like "antidepressants" or "stimulants" which may be confusing – why 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. In addition to the NbN, the NbN-Child & and Adolescent (NbN C&A) was released in 2018.[67] Whilst the NbN C&A is still a work in progress, it is one initiative that should stimulate the implementation of a nomenclature that is less confusing.

Reducing stigma on child and adolescent psychopharmacology

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

CONCLUSIONS

There are certainly significant challenges, but also important opportunities in child/adolescent psychopharmacology that 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 issue, assessing outcomes beyond core symptoms, considering developmental stage, comparing pharmacological and non-pharmacological treatments, using innovative designs beyond standard RCT, moving towards precision medicine/stratification approaches, additional 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.

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DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its Committees or working parties.

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Panel 1: Methodology underpinning this position paper

This position paper summarises the unmet needs and opportunities in terms of the psychopharmacological treatment of child and adolescent mental conditions put forward by the members of the European College of Neuropsychopharmacology (ECNP) - Child & Adolescent Network (ECNP-C&A), alongside experts by lived experience 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 Medicine Agency* (EMA). Initially, each member of the ECNP-C&A was asked to generate a list of unmet needs and priorities. These were then grouped by topic and listed in an initial outline draft that was circulated to the ECNP child and adolescent network, experts by experience representatives (parents and their children), and EMA representatives. In parallel, we held meetings with experts by experience and EMA representatives to discuss and refine the draft. We codesigned a short survey, together with experts by lived experience representatives, approved by the ethics committee of the university of Southampton, UK (ERGO-ID: 75167). This survey was translated into 23 languages and it was circulated to the members of relevant associations located through experts by experience and ECNP-C&A members. The survey included the following questions: *1- What information would you like to see from future studies on the pharmacological treatment of children and adolescents with mental conditions? 2- Do you think there is stigma related to the pharmacological treatment of children and adolescents with mental health conditions? 3- If so, how can we tackle it?*

The initial outline was refined in a series of online meetings among representatives of the ECNP, experts by lived experience associations, and EMA. The outline was then finalised at the meeting of the ECNP child and adolescent neuropsychopharmacology network (Venice, 30 March 2022). 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 13 May 2023) to retrieve: 1) any previous European or international position paper on child and adolescent psychopharmacology; 2) international psychopharmacoepidemiological studies including children/adolescents; 3) umbrella reviews (i.e., quantitative evidence synthesis of meta-analyses/systematic reviews) on the efficacy/effectiveness and tolerability/safety of pharmacological interventions for child and adolescent mental conditions; 4) systematic reviews on relevant compounds in the pipeline (syntax and search terms are reported in Appendix 1).

Panel 2. Recommendations from the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) Working Group on preparedness of clinical trials about paediatric medicines process

- starting early, preferably while designing the medicine's development plan and individual protocols; identifying the rationale and clinical need
- listening to the perspectives of people with lived experience
- determining how many participants will be eligible for the trial
- calculating the resources needed
- using all available data to estimate feasibility
- presenting information about preparedness in a structured way
- deploying appropriate resources to support the preparation of trials

Table 1. Psychotropic medications approved by the European Medicine Agency (EMA) and by the Food and Drug Administration (FDA) for children and adolescents, grouped by indication in alphabetical order. Medications are presented by condition (in alphabetical order).

Table 2. Results of the survey among experts by lived experience (644 participants).

Table 2a. Answer to the survey question: "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?

Table 2b. Answer to the survey question: "In your opinion, do people think that taking medicines for mental problems is bad?

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