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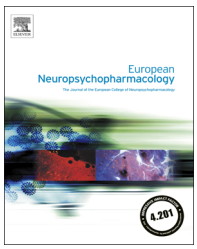

REVIEW

Unmet needs in paediatric psychopharmacology: Present scenario and future perspectives

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Abstract
Paediatric psychopharmacology holds great promise in two equally important areas of enormous biomedical and social impact, namely the treatment of behavioural abnormalities in children and adolescents, and the prevention of psychiatric disorders with adolescent- or adult-onset. Yet, in striking contrast, pharmacological treatment options presently available in child and adolescent psychiatry are dramatically limited. The most important currently unmet needs in paediatric psychopharmacology are: the frequent off-label prescription of medications to children and adolescents based exclusively on data from randomized controlled studies involving adult patients; the frequent lack of age-specific dose, long-term efficacy and tolerability/safety data; the lack of effective medications for many paediatric psychiatric disorders, most critically autism spectrum disorder; the scarcity and limitations of randomized placebo-controlled trials in paediatric psychopharmacology; the unexplored potential for the prevention of psychiatric disorders with adolescent- and adult-onset; the current lack of biomarkers to predict treatment response and severe adverse effects; the need for better preclinical data to foster the successful development of novel drug therapies; and the effective dissemination of evidence-based treatments to the general public, to better inform patients and families of the benefits and risks of pharmacological interventions during development. Priorities and strategies are proposed to overcome some of these limitations, including the European Child and Adolescent Clinical Psychopharmacology Network, as an overarching Pan-European infrastructure aimed at reliably carrying out much needed psychopharmacological trials in children and adolescents, in order to fill the identified gaps and improve overall outcomes.

1. Introduction

All theoretical frameworks to describe and analyse psychological functioning and human behaviour invariably view childhood and adolescence as crucial to the development of life-long mental health and disease. In recent decades, the growth of basic neuroscience has indeed pushed developmental psychology beyond limited descriptions and interpretations of human cognitive, emotional and behavioural trajectories, into a bio-psycho-social framework where the neurobiological underpinnings of typical development hold a key position (Lee et al., 2014; Schumann et al., 2014). Within this framework, the link between abnormal neurodevelopment and paediatric psychopathology has become the object of intense investigation, which holds a realistic promise to produce major advances in developmental neuropsychopharmacology in the not-so-distant future. Furthermore, adult psychiatric disorders have been shown to at least partly stem from neurodevelopmental abnormalities arising from early or late childhood, if not even prenatally (Salum et al., 2010).

Recognizing this great potential for major upcoming progress in clinical practice, but also acknowledging the serious limitations of current psychopharmacological interventions in paediatric neuropsychiatry, the Child & Adolescent Neuropsychopharmacology Network of the European College of Neuropsychopharmacology (ECNP; http://www.ecnp.eu/) held a Targeted Network Meeting (TNM) on October 4, 2013, satellite to the 26th Annual ECNP Congress (Barcelona, Spain). Thirteen experts presented evidence, shared opinions, described policies and debated views around the many unmet needs in child psychopharmacology. In the ensuing year, a dialogue on these subjects was continued by the participants with the goal of producing the present meeting report, which provides a snapshot of the most critical unmet needs, summarized in Table 1, as well as a general framework to guide future collaborative efforts and advance the field of paediatric psychopharmacology.

2. The off-label prescription to children and adolescents of medications with regulatory approval only in adults

Developmental neuropsychopharmacology has progressively evolved from considering youth as “small adults”, to investigating new fields of interest specific to children and adolescents (Arango, 2015). However, to date only very few medications have been approved in Europe for use in children and adolescents (Table 2). Many psychotropic medications prescribed to paediatric patients are unlicensed and off-label. In fact, the vast majority of medicines prescribed to children throughout the European Union (EU) have actually never been studied in this population but only in adults, and not necessarily for the same disease (Conroy et al. 2000). This unlicensed and off-label use conceivably stems from: (i) a dearth of clinical trials in paediatric populations, due to insufficient commercial incentives and/or ethical barriers associated with studies in children and adolescents; (ii) delays in licensing medications for youth, and (iii) lack of suitable formulations for paediatric patients. On the one hand, regulatory authorities have denied registration for the majority of these medications, due to the lack of extensive information on long-term

Table 1 Summary of the unmet needs in current child and adolescent neuropsychopharmacology and proposed solutions.

Unmet needs	Proposed solutions
• The frequent off-label prescription to children and adolescents of medications with regulatory approval only in adults • Insufficient long-term efficacy and safety information in the paediatric population • Off-label prescriptions not always supported by sufficient evidence	• Monitoring the efficacy of EU Regulations n. 1901/2006 and 1902/2006 requiring a Paediatric Investigational Plan (PIP) for all newly marketed drugs, and of the 6-month patent extension granted by the FDA to pharmaceutical companies providing long-term efficacy and safety information for the paediatric population. The ultimate goal should be to promote more "Paediatric Use Marketing Authorizations" (PUMAs) • Pharmacological surveillance through existing electronic anonymized patient-level registries available to healthcare professionals for consultation prior to an off-label prescription of psychoactive drugs to children and adolescents
The lack of effective drugs for many childhood disorders	Promote personalized psychopharmacology by: • developing novel compounds to correct the underlying pathophysiology in patients selected through genetic analysis and biomarker panels • including longer follow-up periods • testing drug × behavioural treatment designs • adopting scales with demonstrated pre-/post-treatment sensitivity
Lack of evidence-based approaches to prevent psychiatric disorders with adolescent-onset	Foster clinical trials on primary and secondary prevention using pharmacological treatments either alone or as part of a multidisciplinary intervention
The need for better preclinical data to foster novel drug therapies	Promote preclinical investigation especially in four areas, namely genetics, new animal models, induced pluripotent stem cells, and epigenetics including miRNAs and non-coding RNAs
Randomized clinical trials (RCTs) have methodological limitations and raise concerns, including:	Randomized clinical trials (RCTs) are the gold-standard in paediatric psychopharmacology, but they can be ameliorated or alternatives can be applied, as follows:
• Limited generalizability due to sample selection criteria	• Encourage phase III/IV trials targeting "real-life" patients (preschoolers, polypharmacy users, cases with comorbidities, etc.)
• Overestimation of clinical benefits produced by the active drug in an "artificial" experimental setting	• After a positive RCT, evaluate effectiveness in practice settings ("large simple trials")
• Inefficiency (expensive, time- and labour-consuming, vexed by high drop-out rates)	• Estimate dose- and time-response relationships by Bayesian simulation and modelling of preclinical and clinical data; use interim data to modify the design in a pre-planned manner (adaptive trial design); take measures to minimize drop-out rates
• Enhanced risk of false-negatives due to high placebo effect	• Reduce the number of recruiting sites, increase the number of cases recruited at each site, pay attention to the geographic distribution of recruiting sites if ethnic dyshomogeneity in response to the active drug is likely, increase the duration of recruitment, reduce pressure by regulatory agencies to complete RCTs as soon as possible regardless of study outcome
• Enhanced risk of false-negatives due to primary efficacy endpoints defined only by a significant decrease in symptom ratings below placebo, to reach a pre-established threshold	• Also apply alternative endpoints (reduction in concomitant psychopharmacological treatments, improved functional measures and quality-of-life ratings, greater efficacy of standardized behavioural therapies); use scales and measures sensitive to change
• Ethical concerns over using placebo in developing individuals who may benefit from the active drug	• Dose-response studies starting with a low drug dose and without placebo • Add-on studies that assess the additional effect of a new treatment in partial responders to standard therapy.

Table 1 (*continued*)

Unmet needs	Proposed solutions
• Enrolment of pathogenetically heterogeneous patients	• Initially collect biomaterials and clinical data to later identify biomarker panels characteristic of responders; later recruit homogeneous subgroups of "probable responders" based on biomarkers
Limited efficacy of current EU legislation on paediatric drug development	• Concerted efforts between regulatory agencies and industry to agree upon incentives sufficient to foster (a) the clinical development of off-patent drugs and (b) the generation of adequate data, meeting criteria set forth by regulatory agencies
Growing resistance to treating children and adolescents with psychotropic drugs in many patient families, medical doctors and in society as a whole	• Develop drugs with unquestionable efficacy on currently untreatable disorders • Define sets of criteria for the establishment and discontinuation of drug treatment • Acquire or expand currently-existing long-term efficacy and safety data • Encourage widespread dissemination by reliable and authoritative agencies, in objective ways and using effective vehicles, including web-based means

Table 2 Psychotropic medications approved in Europe for use in children and adolescents.

Medication	Indication	Age for prescription
Aripiprazole	Schizophrenia	≥ 15 years
	Bipolar disorder, manic or mixed episodes	≥ 13 years
Amphetamines (incl. Lisdexamphetamine)	Attention-Deficit Hyperactivity Disorder[a]	≥ 6 years
Atomoxetine	Attention-Deficit Hyperactivity Disorder	≥ 6 years
Fluoxetine	Major depressive episode	≥ 8 years
Fluvoxamine	Obsessive-compulsive disorder	≥ 8 years
Methylphenidate	Attention-Deficit Hyperactivity Disorder	≥ 6 years
Risperidone	Aggression[b]	≥ 5 years
Sertraline	Obsessive-compulsive disorder	≥ 6 years
Ziprasidone	Bipolar disorder, manic or mixed episode[c]	≥ 10 years

[a]Approved only in some European countries for children and adolescents with ADHD.
[b]Approved only in some European countries for children and adolescents with conduct disorder, in the presence of sub-average intellectual functioning or intellectual disability and when all non-pharmacological strategies have been found insufficient.
[c]Approved only in some European countries based on one randomized controlled trial (Findling et al., 2013), found by the US Food and Drug Administration to have quality assurance issues, requiring the sponsor to repeat the trial.

efficacy and safety in individuals younger than 18 years old, thus leading to their off-label use. In addition to age, also the origin and ethnicity of paediatric cohorts is relevant, because the European Medicine Agency (EMA), while accepting data generated outside the EU, requests that a sizable percentage of paediatric patients be recruited in Europe. On the other hand, the patents of many of these medications have expired, leaving little commercial incentive for pharmaceutical companies to support the clinical trials necessary to achieve registration. These difficulties are by no means limited to the EU, but are indeed present also in North America, so much that the Food and Drug Administration (FDA) devised a 6-month patent extension for pharmaceutical companies providing long-term efficacy and safety information for paediatric population. In the EU, it will be interesting to see in coming years whether and to what extent the new EU Paediatric Regulation requiring a Paediatric Investigational Plan (PIP) for all newly marketed drugs will overcome the paucity of information available in youth and stimulate the achievement of more "Paediatric Use Marketing Authorizations" (see Section 7, for further details).

Meanwhile, during the last decade the rate of prescription of several psychotropic medications to children and adolescents has shown a dramatic increase both in the USA (Olfson et al., 2012, 2014) and also, albeit to a lesser extent, in several EU countries (Rani et al., 2008; Kalverdijk et al., 2008). With the possible exception of

psychostimulants, this increase in prescription rates pertains mostly to the off-label use of second-generation antipsychotics (SGAs) or selective serotonin reuptake inhibitors (SSRIs) (Koelch et al., 2009). Country-specific practices may underlie these trends: in Canada, prescriptions of antipsychotics to youngsters (frequently off-label) are disproportionately higher among general practitioners than among psychiatrists (Murphy et al., 2013), whereas in Germany hospital-based specialists prescribe significantly more antidepressants off-label compared to general practitioners (Dörks et al., 2013). Some data seemingly support this off-label use of SGAs and SSRIs in the paediatric population for at least some indications, while also raising caution on their long-term effects:

(a) *SGAs*. To date, only aripiprazole has received regulatory approval across all of Europe for paediatric indications, namely manic or mixed episodes of bipolar disorder in patients 13–17 years old and schizophrenia in patients 15–17 years old (Table 2). SGAs approved for paediatric use in several, but not all European countries, include risperidone for aggressive behaviour in patients aged 5–17 years with intellectual disability, and ziprasidone for manic or mixed episode of bipolar disorder in youth aged 10–17 years old. A review of 27 studies analyzed efficacy and/or tolerability of SGAs in children and adolescents with bipolar, autism spectrum or disruptive behaviour disorders and indicated greater efficacy for mania, extreme mood variability, irritability, aggression and disruptive behaviour (mainly in patients with co-morbid intellectual disability or borderline IQ) (Zuddas et al., 2011) than in another review of 34 studies for psychotic symptoms in schizophrenia (Fraguas et al., 2011). The average Number Needed to Treat (NNT) for study-defined treatment response was 2–5 for non-psychotic disorders, whereas for schizophrenia the NNT ranged from 3 for risperidone to 10 for olanzapine, quetiapine, and aripiprazole (Correll et al., 2011; Zuddas et al., 2011). As for schizophrenia, different SGAs show similar efficacy also for non-psychotic disorders, but significantly differ in their tolerability and safety profile (Correll et al., 2011; Zuddas et al., 2011). Acute adverse effects of SGAs in children and adolescents are usually minor, predictable and easily manageable (Correll, 2008). However, some adverse events, such as drug-induced involuntary movements, metabolic, and endocrine side effects (i.e., hyperprolactinemia and amenorrhea), occur more frequently in adolescents than in adults (Arango et al., 2014a). In particular, metabolic side effects, increasing the risk for cardiovascular disorders and for type 2 diabetes, may be severe and potentially life-span reducing (Correll et al., 2009; Arango et al., 2014a; Galling and Correll, 2015). Conversely, a clinical diagnosis of a psychotic disorder or even isolated psychotic symptoms also significantly increase the risk of medical conditions (Moreno et al., 2013).

(b) *SSRIs*. So far, only three SSRIs have received regulatory approval in Europe for use in the paediatric population: fluoxetine for moderate to severe major depressive episodes starting at age 8, sertraline and fluvoxamine for obsessive–compulsive disorder after age 6 and 8 (Table 1). No registration has been granted in the EU below age 18 for citalopram, paroxetine, venlafaxine, and duloxetine, although many of these medications are used off-label in several western countries for mood disorders, anxiety, eating disorders and other behavioural disorders of children and adolescents. A recent survey carried out on the German Pharmacoepidemiological Research Database (GePaRD), retrieving data from four German statutory health insurance companies, showed prescription rates of tricyclic antidepressants and SSRIs in 1.57–1.84/1000 children in the years 2004–2006, with 49.1% of the prescriptions being off-label, more often for age than for indication (Dörks et al., 2013). Extensive meta-analyses have shown the relatively modest efficacy of all classes of antidepressants, including SSRIs, in juvenile depression, often related to a high placebo effect, particularly in prepubertal youth (Bridge et al., 2007; Qin et al., 2014). Potential explanations for these results include age-related differences in the neurobiological and psychosocial underpinnings of depression and inadequate study design (i.e., inclusion criteria not sufficiently selective for severity or comorbidity, questionnaires and outcome measures inappropriate for age, lack of a placebo run-in phase before placebo randomization) (Moreno et al., 2007; Usala et al., 2008; Tsapakis et al., 2008). Importantly, in youngsters the efficacy of SSRIs is significantly higher for obsessive–compulsive disorder (OCD) (NNT=6) and, especially, for generalized anxiety disorder (NNT=3) than for juvenile depression (NNT=10) (Bridge et al., 2007), and very comparable to the efficacy recorded for OCD and anxiety in adults (Huhn et al., 2014).

Not all off-label prescriptions are supported by sufficient evidence, which is very concerning. Both in the USA and in Europe, prescription rates of SGAs to patients younger than 18 years of age are significantly higher than the prevalence of psychotic disorders (Rani et al., 2008; Kalverdijk et al., 2008; Zito et al., 2013). In fact, these medications are being prescribed for aggression, irritability, negativistic and hostile behaviour in various conditions, such as autism spectrum disorder, oppositional defiant disorder and conduct disorder (Olfson et al., 2012), when evidence of efficacy in "pure" conduct disorder (i.e., without co-morbid intellectual disability) is limited (Findling et al., 2000). Furthermore, many psychiatric disorders in youth persist across development (Costello et al., 2011), requiring long-term drug treatment. However, regardless of medication class, studies on maintenance treatments generating data on long-term efficacy and tolerability/safety are the exception rather than the rule in paediatric psychopharmacology, and recommendations for treatment type and duration after the acute phase are mostly derived from adult studies.

3. The lack of effective drugs for many childhood disorders

No curative and only few symptomatically effective pharmacological agents are currently available for the treatment of psychiatric disorders with onset in childhood and adolescence. Disorders with the largest unmet needs were identified and prioritized by experts attending the TNM meeting as displayed in Fig. 1, underscoring the critical

importance of finding effective drug treatments especially for autism spectrum disorder, bipolar disorder, anorexia nervosa and other eating disorders, conduct disorder and frequent cross-disorder conditions such as intellectual disability, in addition to several others (see Fig. 1). This issue is of enormous relevance not only for affected youth and their families, but also for National Health Systems (NHSs), considering that most developmental disorders persist into adulthood (Costello et al., 2011).

Autism spectrum disorder (ASD) was deemed by the experts as the number one unmet need (Fig. 1). Effective pharmacological treatments for the core symptoms of this severe and highly impairing condition with childhood onset are indeed still lacking. Despite considerable progress in understanding the neurobiology of ASD (Parellada et al., 2014), educational and behavioural interventions still remain the only viable therapeutic strategies able to variably ameliorate core autistic symptoms, while pharmacological intervention has shown efficacy only on comorbid conditions or related symptoms (Politte et al., 2014). In particular: (a) psychostimulants have been proven effective in reducing the hyperactivity and impulsivity, present in up to a third of ASD cases (Simonoff et al., 2008; Harfterkamp et al., 2012). Their efficacy is somewhat lower compared to effects in children with "pure" ADHD, while side effects (i.e., irritability, lethargy, tics, sadness, and social withdrawal) tend to be more frequent and severe in autistic children with comorbid ADHD (Research Units on Paediatric Psychopharmacology Autism Network, 2005; Simonoff et al., 2013); (b) SGAs, particularly risperidone and aripiprazole, have been shown to control irritability, agitation, compulsions and aggressiveness, with evidence of maintained efficacy for up to 6 months of treatment in the majority of patients (Marcus et al., 2009; Politte and McDougle, 2014; Zuddas et al., 2011); (c) SSRIs display some efficacy on anxiety and repetitive behaviours in adults, but not in children and adolescents with autism (Williams et al., 2010). This lack of efficacy in the paediatric ASD population is likely related to age-specific differences in underlying neurobiological mechanisms, to target symptoms (autistic individuals report anxiety as distressing and stereotypic behaviours as relaxing), and to the use of assessment tools and outcome measures that have been validated only in individuals without ASD (Reiersen and Handen, 2011). As evident from this brief summary, the core symptoms of ASD in children and adolescents (i.e., deficits in social interactions and communication, stereotypic behaviours, insistence on sameness, abnormal sensory processing) still remain outside the direct targets of currently available pharmacological approaches.

Despite the genetic complexity underlying ASD, the number of pathophysiological processes involved in abnormal neurodevelopment being potentially amenable to pharmacological modulation may be relatively limited (Persico and Napolioni, 2013; De Rubeis et al., 2014; Pinto et al., 2014). To date, drug development strategies aimed at correcting the pathophysiological abnormalities underlying ASD have primarily taken the move from single-gene disorders that are frequently comorbid with autism, ultimately leading to phase I-III studies initially aimed at treating the original single-gene disorder, but subsequently or currently targeting ASD (Fig. 2). Experimental therapies relevant to ASD have been recently reviewed (see Table 1 in Vorstman et al., 2014; also see Vitiello and Grabb, 2013, and www.clinicaltrials.gov). Promising results in humans have already been communicated for some of these drugs, when applied in cohorts of patients with ASD-associated genetic disorders (Franz et al., 2014; Jacquemont et al., 2011, 2014; Khwaja et al., 2014), whereas initial phase II/III trials performed to date in patients with ASD have failed to meet their end-points (see Veenstra-VanderWeele et al., 2013, abs. 102.001; Kaufmann et al., 2013, abs. PS1-6). This disappointing outcome may be attributable to several reasons, including (a) administration of a single experimental drug to heterogeneous groups of patients, regardless of their different underlying pathophysiology; (b) short trial durations; (c) lack of controlling for and/or associating specific behavioural interventions or rehabilitation programs; (d) using scales at times not sufficiently sensitive to detect meaningful pre-/post-treatment change; and (e) treatment possibly outside of the critical period of maximum brain plasticity in the developmental trajectory of the patient.

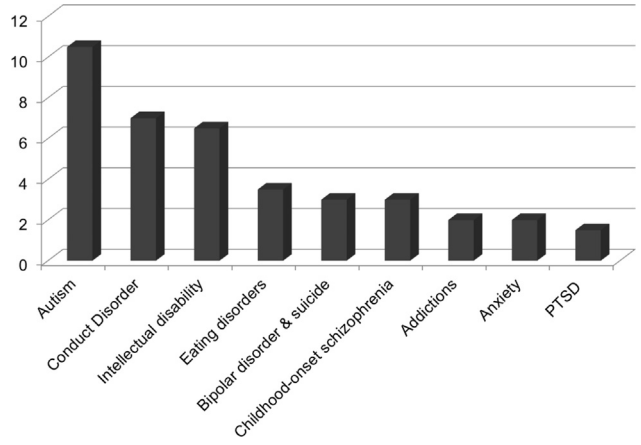

Fig. 1 Priority order for drug development in child and adolescent psychiatry by disorder or condition. Each expert attending the ECNP Targeted Network Meeting was awarded three priority options and ordinate values represent raw counts of disease priorities.

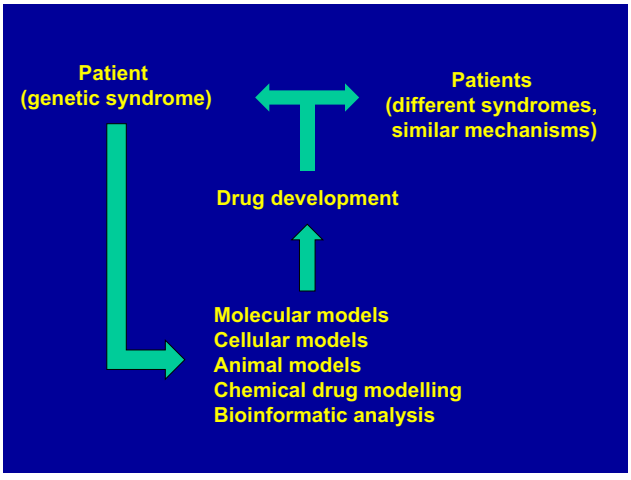

Fig. 2 Translational approach to paediatric psychopharmacology, starting from the characterization of rare genetic syndromes and applying discoveries to more common and often comorbid disorders (see text).

A paradigmatic example of the challenges posed to experimental human psychopharmacology by ASD is represented by studies investigating the use of antagonists at the metabotropic glutamate receptor type-5 (mGluR5). Approximately 50–67% of boys and 20–23% of girls with Fragile-X syndrome (FraX) also meet diagnostic criteria for ASD as evidenced by well validated instruments (ADOS-G, ADI-R or both) (Clifford et al. 2007; Hall et al., 2008). FraX is due to the expansion of a CGG triplet-repeat located in the promoter of the FMR1 gene, which produces its methylation and transcriptional shut-down (Fu et al., 1991). The FMR protein (FMRP), encoded by the FMR1 gene, negatively modulates translation locally at the synaptic level by binding a variety of mRNAs and making them unavailable to the translational machinery (Eberhart et al., 1996). Fmr1-ko mice were then shown to display abnormal long-term depression due to excessive mGluR5 signaling and internalization of AMPA glutamate receptors: the "mGluR theory" of FraX thus lays the foundation of FraX pathophysiology upon three consequences of the absence of FMRP, namely: (a) excessive mGluR1/5 stimulation, (b) enhanced local protein synthesis, and (c) undue internalization of AMPA receptors (Bear et al., 2004). Indeed, a remarkable reversal of excessive protein synthesis, dendritic spine alterations and abnormal behavioural phenotypes was observed in Fmr1-ko mice by blunting mGluR5 signaling through genetic strategies (Dölen et al., 2007) or by administering the mGluR1/5 antagonist MPEP (Yan et al., 2005; de Vrij et al., 2008). Despite this wealth of preclinical evidence strongly supporting the promising efficacy of mGluR5 antagonists in FraX and possibly in ASD, one preliminary clinical study of an mGluR5 antagonist failed to reach its endpoints in adult FraX subjects, though showing some promise in the subgroup of patients carrying complete methylation of the FMR1 promoter (Jacquemont et al., 2011). Several explanations were put forward to explain the limited success of mGluR5 antagonists in FraX, namely patient heterogeneity, lack of reliable markers to predict treatment response and side effects, outcome measures displaying low sensitivity to change, short trial duration and the use of a pharmacological intervention alone in the absence of a controlled behavioural treatment (Jacquemont et al., 2014). Particularly critical appears the notion that if patient heterogeneity raises concern in studies of a monogenic disorder like FraX, this concern is aggravated in polygenic ASD. Further clinical studies with these medications are absolutely necessary before firm conclusions can be drawn, as the use of mGluR5 antagonists still represents a logical and scientifically-founded approach. Yet, based on initial trials, ongoing and future investigations will likely benefit from selecting patients according to their underlying pathophysiology defined through biomarker panels, including longer follow-up periods, testing drug × behavioural treatment designs, and adopting scales with demonstrated pre-/post-treatment sensitivity (Jacquemont et al., 2014; Lee et al., 2014; Ruggeri et al., 2014).

4. In search for evidence-based approaches to prevent psychiatric disorders with adolescent-onset

Adolescence is a period of extraordinary physical, psychological and social growth: personal and gender identity, morals and ideals, relationships with peers and adults, all undergo major reshaping to finalize their developmental trajectory and form a fully "adult" self. Major hormonal and neurobiological changes underlie these phenomena: following overproduction of synapses during childhood, adolescence fosters the selection and stabilization of relevant synaptic contacts, paralleled by prominent synapse elimination under the influence of sex hormones. The number of synaptic contacts decreases by as much as 50% on average at age 16 compared to early childhood (Huttenlocher, 1979). This synaptic remodelling profoundly affects neuronal circuitry, especially in the prefrontal cortex, as well as the excitatory/inhibitory neurochemical balance. Meanwhile, the completion of myelination finalizes the structural and functional connectivity underlying adult emotional and cognitive processing, including executive functions (working memory, self-regulation of affect-motivation-arousal, internalization of speech, and behavioural analysis and synthesis). Individuals vulnerable to disruptions of healthy development are at special risk during this time: in fact, many adult psychiatric disorders become manifest by age 14 and the large majority by age 24 (Kessler et al., 2005). The association with prenatal and perinatal hazards, the high frequency of minor neuro-motor abnormalities and physical dysmorphisms, presence of minor structural brain abnormalities both predating and contemporary to the emergence of behavioural symptoms, and absence of neurodegeneration in post-mortem brains, all collectively support the neurodevelopmental hypotheses put forth to explain severe disorders with onset during adolescence or early adulthood, such as schizophrenia (Arango et al., 2012, 2014b). In brief, a general consensus currently views pre- and perinatal development as a critical period when genes and environmental factors can interact in vulnerable individuals to produce functional and structural abnormalities that often become evident only later during adolescence or early adulthood. In the case of schizophrenia, different genetic pathways have been identified (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), while early social stress, drugs of abuse, inflammation and oxidative stress appear to act as environmental modulators or triggers (Fraguas et al., 2012; Horváth and Mirnics, 2015). The long latency between pre-/perinatal damage and the onset of behavioural abnormalities in adolescence spurs interest into primary prevention of the full-blown disorder, provided reliable biomarkers of vulnerability and early damage are established, as well as a better understanding of pathogenic and resilience factors, as well as their mutual interactions. Studies exploring the potential efficacy of medications able to attenuate neuroinflammation and oxidative stress in the CNS (e.g., glutathione, *N*-acetylcysteine, sulforaphane, polyunsatured fatty acids, glycine agonists, etc.) have yielded promising preliminary results in a wide variety of psychiatric and neurodevelopmental disorders (Amminger et al., 2015; Chue and Lalonde, 2014; Pandya et al., 2013; Singh et al., 2014).

The search for preventive strategies through pharmacological therapy is not at all new in paediatric neurology and psychiatry. An example of primary prevention is represented by magnesium sulfate administration to women at risk of preterm birth before 30 weeks' gestation, where it has been shown to significantly reduce the incidence of cerebral palsy and gross motor skill deficits in the offspring (Crowther

et al., 2003). More often, psychopharmacological treatment applied early on, usually as part of a multidisciplinary therapeutic intervention, has been shown to confer secondary prevention by diminishing unfavourable developmental trajectories, otherwise leading to severe complications or to additional disorders. A consolidated example is ADHD as a risk factor for deviant behaviour (Barkley et al., 2004). In a population-based study, treatment with ADHD medications (methylphenidate, amphetamine, dexamphetamine or atomoxetine) was shown to reduce criminality rates by as much as 31% and 41% in convicted men and women, respectively, compared to unmedicated periods (Lichtenstein et al., 2012). Also relapse in substance abuse was reduced in addicted criminal offenders undergoing methylphenidate treatment (Konstenius et al., 2014). Similarly, methylphenidate treatment significantly reduces the risk of trauma requiring emergency department admission in ADHD (Man et al., 2015). Preventive opportunities are also offered by novel medications such as everolimus, which seemingly ameliorates not only treatment-refractory epilepsy in tuberous sclerosis, but also behaviour and quality-of-life (Krueger et al., 2013). Nonetheless the important area of primary prevention in schizophrenia is still in its initial stages, as only preliminary, but certainly not conclusive evidence of effective preventive treatments has been obtained so far (Correll et al., 2010).

5. The need for better preclinical data to foster novel drug therapies

The importance of preclinical data in setting the stage for appropriately targeted and well-designed clinical trials has clearly emerged in previous sections. Here, we shall focus on four specific approaches, namely genetics, animal models, induced pluripotent stem cells (iPSC), and non-coding RNAs. Each represents a promising preclinical avenue for the advancement of child psychopharmacology, but each also presents with limitations and caveats.

(A) Human genetics represents one major foundation upon which drug discovery is being built through multiple translational approaches. The past two decades have seen a tremendous progress in understanding the genetic architecture of developmental psychopathology, which involves both rare and common genetic variants. The number of identified genetic variants associated with neuropsychiatric disorders has been rapidly increasing, both in terms of rare variants typically exerting a large impact on disease risk in few or even single patients, and of common variants, individually of small impact but collectively of large effect on disease risk through the cumulative effect of many different variants in many individuals (Vorstman and Ophoff, 2013). Indeed, the proportion of patients with identified genetic abnormalities is currently estimated at approximately 20% in ASD (Jeste and Geschwind, 2014) and 40% in intellectual disability (Topper et al., 2011), a substantial increase in comparison to the situation in the not-too-distant past. Conversely, up to 30% of undiagnosed children with developmental disorders can be correctly diagnosed by a combination of whole-exome sequencing and array-based search for chromosomal rearrangements (The Deciphering Developmental Disorders Study, 2015). Importantly, the increasing number of identified risk genes appears to converge on a smaller number of biological pathways (Persico and Napolioni, 2013; De Rubeis et al., 2014; Pinto et al., 2014), thereby providing novel insights into the underlying biology of these disorders. Examples include the mTOR pathway, chromatin regulation and synaptogenesis (Persico and Napolioni, 2013; De Rubeis et al., 2014; Pinto et al., 2014; Vorstman et al., 2014) in autism, neuronal migration in intellectual disability (Liu, 2011) and glutamate signaling in ADHD (Elia et al., 2011). An important consequence of these advances is the possibility to identify potential novel pharmaceutical agents based on the growing insight into the implicated biological pathways (Ghosh et al., 2013; Vorstman et al., 2014). In addition, as the number of associated risk variants continues to increase, the possibility of using individual genetic information as a means of treatment stratification may become feasible. For example, a recent study has reported distinct neuronal bases of ADHD, depending on MAOA genotype (Nymberg et al., 2013). Also, behavioural heterogeneity may be reduced when patients are stratified in accordance to genetic characteristics (Bruining et al., 2014). Possibly, the first clinical implementation of genetic stratification strategies may be their use in predicting treatment response and/or adverse side effects of existing psychopharmacological treatments. Proof of principle has been shown for several genotypes associated with, amongst others, the risk of agranulocytosis in clozapine (Athanasiou et al., 2011) and the likelihood of antidepressant treatment response to SSRIs in adults (Fabbri et al., 2014). Finally, going one step beyond genes into the realm of developmental transcriptomics may allow the definition of the critical periods of greatest disease risk and therapeutic sensitivity based on each individual's underlying genetics and neurobiology (Tebbenkamp et al., 2014).

Despite these perspectives, considerable challenges need to be resolved before insights from genetic studies can be translated into useful applications in clinical practice: (a) genetic contributions to neurodevelopmental disorders remain elusive in the majority of patients; (b) for the vast majority of currently identified genetic risk variants, penetrance is far from complete and probably modulated by other genetic variants (Leblond et al., 2012; Steinberg and Webber, 2013), as well as by epigenetic dysregulation dependent on parental age at conception and/or environmental factors (Berko et al., 2014; Frans et al., 2013; Persico and Merelli, 2014); (c) more than one biological pathway may be implicated in single patients, thus possibly requiring drug combinations for targeted treatment; (d) many genetic risk variants lack disease specificity, conferring vulnerability toward a range of different neuropsychiatric and developmental disorders (Smoller, 2013); (e) stratification and/or prediction of treatment response of sufficient reliability likely require the use of genome-wide genotype and CNV profiles, covering the entire spectrum of rare to common genetic and genomic variants, instead of information derived from single genotypes. These

challenges underscore the need to foster the parallel growth of knowledge into genetic and epigenetic variants conferring disease vulnerability and of preclinical models able to summarize the functional derangements triggered by those variants.

(B) Preclinical modelling plays a crucial role in fostering successful drug development. "Traditional" animal models have, on the one hand, provided a wealth of useful neuroanatomical, neurochemical, electrophysiological, developmental and behavioural information; on the other hand, limitations in face, construct and predictive validity must be duly acknowledged, as they may in some cases have contributed to the failure of some drug development programs. Such failures may have occurred particularly when investigators have assumed animal models to reproduce human disorders, rather than specific symptoms, traits or domains, or when human traits have been projected onto animals with insufficient consideration for species-specificity (Kas et al., 2014). Confidence in positive findings can be increased by the incorporation of multiple readouts of construct validity in the same experimental model. For example, optogenetics can be combined with oxygen biosensors and fMRI BOLD, which is matched onto appropriate behavioural testing analogous to similar human tests (Kas et al., 2014; Weitz et al., 2015). Meanwhile, preclinical researchers should be ready to critically evaluate the validity of some long-held animal models, when positive findings in the animal model have not resulted in equal success in clinical trials.

(C) The last decade has seen the spurt of novel experimental approaches complementary to animal models, ranging from chemogenomic modelling (i.e., matching the target protein sequence with different chemical domains of putative drugs) to bioinformatic tools capable of defining functional gene networks underlying complex behavioural disorders, as well as therapeutic drugs potentially able to target those processes (Poelmans et al., 2011, 2013). One of the most promising experimental paradigm currently under scrutiny employs induced pluripotent stem cells (iPSC) to model human disease (Kitchener and Wu, 2015): differentiated cells, such as fibroblasts or epithelial hair bulb cells, can be transformed into pluripotent stem cells following retrovirus-mediated transfection with the transcription factors c-Myc, Sox2, Oct 3/4, KLF4 (Yamanaka, 2008). Subsequently iPSCs can be differentiated into specific cell types of interest, including neurons. Alternatively, differentiated cells can be reprogrammed directly into neurons by transfecting the four factors Ascl1, Brn2, Myt1l and NeuroD1 (Vierbuchen et al., 2010). The developmental and functional abnormalities present in differentiated neurons in vitro are then predicted to reflect the whole array of rare and common genetic variants present in the patient's genome, rather than the effect of a single mutation or CNV on a different genome. Once these abnormalities are clearly defined, iPSCs or iNEURONS can then be tested for responsiveness to specific psychoactive drugs. As an example, iPSC-derived neurons obtained from fibroblasts of patients with schizophrenia display decreased neurite number, reduced neuronal connectivity, and abnormal gene expression related to glutamate receptors, cytoskeletal remodelling and oxidative stress; at least some of these parameters respond to antipsychotic treatment (Brennand et al., 2012). Several experimental paradigms involving iPSC or iNEURON models of neurodevelopmental disorders have been published to date, underscoring the heuristic potential of this approach (Krey et al., 2013; Cocks et al., 2014; Doers et al., 2014). Meanwhile, several major limitations must be duly acknowledged: (a) the most consistent and reliable transformation protocols have yet to be ultimately defined; (b) the entire process has low efficiency, is cumbersome, bears high costs and takes a long time; (c) the dysfunctional features observed in iPSC-derived neuronal cells may partly be induced by the experimental procedure, which employs oncogenes as reprogramming factors, retroviral vectors for gene transfer and multiple manipulations potentially capable of producing spurious epigenetic abnormalities. Searching for anomalies already in neural tube-like "rosettes", which form as early as on culture day 15 (Lo Sardo et al., 2012; Harding et al., 2014), may represent an informative strategy for at least some neurodevelopmental disorders, while minimizing spurious effects due to later manipulations. Care must be taken, however, in the choice of in vitro readout used to predict validity of test compounds in iPSC neurons and while a number of candidate assays are available, including electrophysiological and morphological changes, there is presently little consensus on the ideal in vitro test battery for drug screening.

(D) Another promising area of investigation is represented by long non-coding RNAs (van de Vondervoort et al., 2013; Meng et al., 2015) and especially by microRNAs (miRNAs), small non-coding RNA molecules essential for neuronal integrity, as clearly exemplified by the progressive cerebellar neurodegeneration and ataxia present in cell-specific dicer conditional knockout mice, unable to produce miRNAs in Purkinje cells (Schaefer et al., 2007). MiRNAs are known to regulate multiple neurodevelopmental processes and several miRNAs regulate the expression of multiple genes relevant to neurodevelopmental disorders (Lett et al., 2013; Meza-Sosa et al., 2014). As an example, miRNA 124 and 195 are both implicated in autism, each modulating multiple targets and thus affecting several autism genes (Vaishnavi et al., 2013). Finally, miRNAs are amenable to pharmacological modulation through drugs defined "antagomirs", which can bind and antagonize miRNAs (Krützfeldt et al. 2005; Ghelani et al., 2012). Also long non-coding RNAs should be considered as a promising therapeutic target for specific neurodevelopmental disorders (Meng et al., 2015). The inclusion of small and long non-coding RNAs into computational models is predicted to greatly enhance their capacity to explain complex phenotypes, to point toward potential therapeutic avenues and to yield biomarkers that may be able to stand as surrogate end points in clinical trials.

6. Paediatric clinical trials: Methodological issues, problems and potential solutions

Randomized clinical trials (RCTs) have contributed remarkably to paediatric psychopharmacology. We can now legitimately

talk of evidence-based psychopharmacology for children and adolescents because dozens of RCTs have investigated the benefits and tolerability/safety of various psychotropic medications during development. While the epistemological value of RCTs in paediatric psychopharmacology is undeniable, two main types of concerns have emerged over this experimental design:

(a) The external validity of RCTs has been questioned, because sample selection and the experimental nature of the studies both limit the generalizability of their results. In simple terms, finding a statistically significant difference between medication and placebo on a symptom rating scale after a few weeks of treatment in a research setting and in a highly selected sample of patients does not adequately inform about the therapeutic benefit or tolerability/safety of the medication when used under usual clinical conditions and for extended periods of time. Patient selection in RCTs is typically restricted to "pure", uncomplicated cases, while "real-life" patients presenting with polypharmacy, suicidal ideation, co-morbid intellectual disability or self-injurious behaviour, just to name a few, are typically excluded; they should instead represent a "special-interest" group, worthy of targeted phase IV trials, which are currently not required at all for labelling authorization. Data collected in adults suggest that RCTs may overestimate the effect size of clinical benefits produced by the active experimental drug, as compared to observational studies (Naudet et al., 2011; Wisniewski et al., 2009). This concern is not new, and it has been generally agreed that traditional RCTs, which establish initial efficacy, should then be followed by practical trials ("large simple trials"), in order to evaluate effectiveness in practice settings (Geddes, 2005). However, few practical trials have been conducted in paediatric psychopharmacology, primarily due to funding limitations and lack of appropriate logistic infrastructure. In reference to age, preschoolers are clearly an understudied population;
(b) The operative implementation of RCTs, as currently conducted, is burdened by a high perceived degree of inefficiency. From an industrial perspective, RCTs are increasingly expensive and extremely time- and labour-consuming. On the one hand, recruiting children and adolescents for double-blind placebo-controlled medication trials has also become more difficult over time. On the other hand, RCTs are often marred by high drop-out rates. Sample sizes are thus often too small to provide the statistical power needed to detect small- or even medium-size effects, which unfortunately represent the typical outcome of pharmacological treatments in psychiatry (Huhn et al., 2014). Furthermore, placebo effects have progressively grown over the years often blunting treatment effects and making RCTs inconclusive. For example, recent studies failed to show separation from placebo on the CDRS-R at 10 weeks for both the investigational drug (duloxetine) and the planned active control (fluoxetine) (Emslie et al., 2014; Atkinson et al., 2014). Importantly, one factor associated with high placebo response is the number of clinical sites involved in an RCT: the greater the number of sites, the larger the placebo response (Bridge et al., 2009). Hence, increasing the number of recruiting sites, each providing only a few subjects, likely contributes more error than valid information, decreasing rather than increasing experimental sensitivity despite larger sample sizes. Contrary to this notion, on average the number of sites involved in RCTs has been progressively growing and it is not uncommon to encounter studies including more than 60 recruiting sites, often spread across different countries and continents (Atkinson et al., 2014). This trend is largely due to regulatory pressure toward RCT completion as soon as possible regardless of study outcome, cost containment and an attempt to maximize sparing of patent protection time by counteracting slow patient recruitment, especially for conditions for which treatments are available in the community, such as depression and anxiety. Not surprisingly, given these premises, most RCTs of antidepressants in children and adolescents are failed or inconclusive trials.

Besides these two major concerns, other considerations are also relevant to the development and testing of psychopharmacological treatments. Primary efficacy endpoints in RCTs, typically represented by a statistically significant decrease in symptom ratings compared to placebo below a pre-established threshold, often oversimplify the complexity of childhood psychiatric disorders and enhance the risk of false-negative results. Alternative endpoints should be considered when regulatory agencies and pharmaceutical companies agree upon a paediatric investigational plan. For example, valuable endpoints for paediatric clinical trials, even in the absence of statistically significant decreases in symptom scores, could well include: (i) a dosage decrease or discontinuation of concomitant psychopharmacological treatments; (ii) consistently improved functional measures and quality-of-life ratings; and (iii) more rapid and favourable improvements produced by standardized courses of behavioural therapies. Furthermore, the targets of treatment are broad and not precisely defined from a neurobiological point of view. Despite remarkable advances in brain imaging, neurocognitive assessment, molecular biology, human genetics and basic neuroscience, treatable psychiatric disorders still represent heterogeneous categories defined only by behavioural symptoms, in the absence of homogeneous neurobiological underpinnings identifiable through valid biomarkers. This limitation affects RCTs at two levels: it leads to the enrollment of heterogeneous samples and to the assessment of treatment effects through subjective rating scales. It is not surprising that, under these circumstances, results are too often inconclusive.

For all of the reasons summarized above, though RCTs still represent the gold standard method for demonstrating the efficacy of new medications, research into alternative methodological approaches should be encouraged. Below are some examples already in use:

a) The use of placebo has been heavily debated in terms of its real need and ethical acceptability. In general, the use of a placebo-arm is considered ethically justifiable when needed to answer appropriate and necessary scientific questions that cannot be answered in any other way, and when risk for the patient is acceptable (March et al., 2004). There are, however, alternatives to the

traditional placebo-controlled design, such as dose-response studies without a null dose (i.e., placebo) or with a very low dose (i.e., faux or pseudo placebo), or add-on studies that assess the additional effect of a new treatment in partial responders to standard therapy (March et al., 2004). These designs could be more acceptable to parents, facilitating children recruitment, and be more ethically justifiable especially in drug trials of longer duration, where children entered into the placebo arm could drop out or conceivably run the risk of growing out of a developmental stage of maximum therapeutic responsiveness.

b) Greater efficiency and cost-effectiveness can potentially be achieved through simulation and modelling of preclinical and clinical data applying Bayesian methodologies to estimate dose-response and time-response relationships for both drug efficacy and safety (Orloff et al., 2009). Adaptive trial designs make use of interim data to modify the design in a pre-planned manner, without affecting its validity and integrity (Orloff et al., 2009).

c) Establishing efficacy of a new medication at the individual and group level may also be facilitated by incorporating validated biomarkers into RCTs (Vorstman et al., 2014). This approach includes the need for *stratification* biomarkers that indicate which patient groups may benefit from a particular treatment; *mechanistic* biomarkers that reflect differences in underlying pathophysiology key to the disorder, and *substitute endpoint* biomarkers that predict later clinical response to drug treatment (Ruggeri et al., 2014; Loth et al., 2015). These biomarkers can be drawn from multiple levels ranging from basic biology (genomic, epigenomic, transcriptomic, proteomic, and metabolomics) to more complex levels closer to brain function (electrophysiology, brain imaging, eye tracking, neuropsychological testing, etc.). So far, few if any biomarkers have been validated and accepted by regulatory bodies for studies in child and adolescent psychiatric disorders (Manolis et al., 2015). The Innovative Medicine Initiative consortium EU-AIMS (European Autism Interventions—A Multicentre Study for Developing New Medications, www.eu-aims.eu) has sought and obtained advice and guidance from the EMA to examine and validate eye-tracking, cognitive, EEG, MRI and biochemical biomarkers for the study of ASD (Loth et al., 2015).

In the meantime, existing electronic anonymized patient-level registries should be constantly enriched with clinical records and monitored by healthcare professionals to a much greater extent, in order to assist them with making the most appropriate therapeutic decisions when prescribing off-label medicines in paediatric clinical practice. Relevant examples in Europe include:

- The French multicenter prospective naturalistic study of adverse events of antipsychotic treatment in naïve children and adolescents, funded by French National Agency for Medicines and Health Products Safety (Menard et al., 2014; id. NCT02007928 on www.clinicaltrials.gov);
- SENTIA: a systematic online monitoring registry for children and adolescents treated with antipsychotics, supported by the Spanish Ministry of Health and Social Politics (Palanca-Maresca et al., 2014);
- The German large simple trial (phase IIIb) about the off-label use of antipsychotics and antidepressants, prospective data collection by an internet-based patient registry, supported by the German Federal Institute of Drugs and Medical Devices (Egberts et al., 2015).

7. The regulatory context of paediatric psychopharmacology in Europe: Strengths and limitations

To address the need for more and better-quality clinical trial data in paediatric medicine, a strategic plan was developed and a new EU Paediatric Regulation came into force in 2007 (Regulations EC nos. 1901/2006 and 1902/2006, available at http://www.ema.europa.eu/). On the one hand, pharmaceutical companies were legally obliged to perform studies in paediatric patients if they intended to develop medicines for use in the adult population, and to prepare a paediatric drug development plan, the "Paediatric Investigational Plan" (PIP). On the other hand, incentives were created for the pharmaceutical industry to test medicines in children and adolescents, namely a 6-month extension of the "Supplementary Protection Certificate" (SPC) including for adult use, and a 10-year extension of the "Paediatric Use Marketing Authorization" (PUMA) in the case that authorized products are no longer covered by intellectual property rights. In parallel, the European Commission (EC) released in 2006 a document on ethical considerations for clinical trials performed in children (available at http://ec.europa.eu/health/files/paediatrics/docs/paeds_ethics_consultation20060929_en.pdf).

The EU Paediatric Regulation has three main objectives: (1) to promote high quality research aimed at maximizing the quality, safety and efficacy of medicines prescribed to children and adolescents, up to and including 17 years of age; (2) to provide more information on the use of paediatric medicines, and (3) to allow the authorization of medicines for diseases that affect youth, with age-appropriate pharmaceutical forms and composition (formulation). As a positive result, in the period between 2007 and 2012 the EMA and its Paediatric Committee have agreed with pharmaceutical companies on more than 600 PIPs, to provide data on the efficacy and safety of medicines for all diseases of children and adolescents (European Medicines Agency, 2013c). The proportion of RCTs involving youth has increased to approximately 10% of the total (European Medicines Agency, 2013a). To foster collaboration within and outside the EU, the EMA has also created "Paediatric Research Networks" (Enpr-EMA), involving the regulators, academia, the pharmaceutical industry, and patient associations (see below). Nonetheless, the fact that only one PUMA has been granted since 2008 indicates that this regulatory context may still not provide adequate incentives to the industry for the clinical development of off-patent drugs (Schmäl et al., 2014).

Regulatory guidelines for the clinical investigation of medications for the treatment of psychiatric disorders such as ADHD, schizophrenia and major depression have been

issued by EMA, while guidelines for investigation of medications for ASD are currently being developed (European Medicines Agency, 2010, 2012, 2013b, 2013c). For confirmatory clinical trials, these guidelines specify at least two randomized double-blind parallel-group design studies with generally three arms: the new target medication, placebo, and an active comparator. The duration of the trials should be at least 6 weeks. In case of short-term efficacy, maintenance of effect and long-term safety should be demonstrated in a randomized withdrawal design. Responders are randomized to either continue treatment with the target medication or switch to placebo for at least 6 months. Responders are then further maintained on medication in open-label fashion for a sufficient period of time, in order to collect tolerability/safety data. An alternative for demonstrating long-term maintenance efficacy and safety is a 6-month randomized double-blind placebo-controlled parallel group study. If relevant, studies should be sufficiently powered to allow for separate analyses of children (6–11 year) and adolescents (12–18 year). The primary outcome measures should: (a) be based on clinicians' ratings, complemented with ratings by significant others such as parents and teachers, and whenever possible by self-reports, especially in the case of adolescents, and (b) include not only symptom intensity scores, but also functional measures and quality-of-life ratings. The clinical investigation designs proposed in these guidelines present all the strengths and limitations of RCTs discussed in the previous section.

8. Limited public acceptance of treating children with medications

Until not too long ago, in many European countries the treatment for child and adolescent psychiatric disorders was largely confined to behavioural and psychosocial interventions. The use of psychotropic medications remained a relative rarity through the 1990s. Afterwards, a rapid increase in prescription rates has occurred, especially for methylphenidate (Dalsgaard et al., 2013) and, to a lesser extent, for SGAs (Steinhausen, 2015; Olfson et al., 2012). Reservations around medication treatment for ADHD have been expressed both in society at large and within the medical profession for many years (Ruel and Hickey, 1992; Zwi et al., 2000). On a broader scale, treating children and adolescents with psychotropic drugs has encountered growing resistance in many patient families and in society as a whole: the media have become increasingly critical about the use of medications in children and adolescents, particularly for psychiatric disorders (Thomas et al., 2013; Partridge et al., 2014); at least in some countries, parents tend to favour psychological treatments, cognitive training, or natural remedies (often not evidence-based) as a means of "steering away from pharmacology" more than was the case 10 years ago; society, media and even health professionals, including many paediatricians, have become more critical and cautious about medication effects on the developing brain.

Several reasons may account for this changed appreciation of medication treatment in child psychiatry. First, the steep increase in prescription rates has led to worries of possible overdiagnosis and overtreatment, fuelled initially by a purported lack of clear-cut boundaries between health and disease in psychiatric disorders and, more recently, by the introduction of DSM-5 (Batstra and Frances, 2012; Pierre, 2012). Second, this potential overtreatment has been viewed by some as having been driven more by commercial pressure from pharmaceutical companies than by real medical need (Watson et al., 2014). Third, long-term treatment duration is often not supported by sufficient data on effectiveness and safety (Molina et al., 2009). In the case of methylphenidate, there is only retrospective evidence of effectiveness beyond two years of long-term use (Barbaresi et al., 2014), but prescription in clinical practice often extends beyond this duration. Long-term methylphenidate treatment has led to concerns about the risk of altering children's personality, but also about adverse effects on sleep, appetite and growth, as well as potential draw-backs regarding the nervous and cardiovascular systems (Gerlach et al., 2013; Germinario et al., 2013; Murray et al., 2013; Awudu and Besag, 2014; see ADDUCE project below). Lastly, these criticisms are often part of an ideological view centred around the concepts of ecology, sustainability, environmental concern and healthy natural remedies, ultimately purporting the damaging effects of anything "artificial" or "man-made"on human health.

What lessons can be learned? As discussed above, the availability of novel pharmacological agents not just effective, but capable of "making the difference" in patients' lives is a critical point. Even today, the same parents who are adamantly opposed to the prescription of psychotropic drugs to their child for behavioural or psychiatric indications, typically accept with ease the prescription of antiepileptic drugs after a first convulsive episode, because epilepsy is perceived as a "severe disorder" and antiepileptic drugs are assumed to be very effective. Equally important is the acquisition of good quality data regarding long-term efficacy and tolerability/safety which may contribute to shift public opinion towards greater acceptability of medication treatments for children and adolescents with psychiatric disorders. More attention should also be devoted to the development and implementation of monitoring guidelines for longer-term treatments, as typically applied in clinical practice. Evidence-based guidance is also needed regarding when and how psychotropic medication should be discontinued. Stopping strategies, as well as defining treatment refractoriness, are two somewhat neglected areas in the field of child and adolescent psychiatry. Finally, all useful drug-related information should be disseminated: (a) by reliable and authoritative agencies, (b) in objective ways (i.e., steering away from both commercial interests and ideological oppositions), and (c) reaching both patients and prescribers also using popular and captivating vehicles, frequently web-based and close to current end-users.

9. European collaborative efforts and future directions

The issues and problems presented in each section of this article need specific solutions, which require a solid and overarching logistic infrastructure at the European level and beyond, fostering intense collaboration among clinicians and scientists with diverse cultural approaches, clinical

background and pre-clinical expertise. This infrastructure can then in turn implement innovative strategies to generate and analyze large biological databases, and to translate innovation into clinical practice.

An initial stimulus toward the generation of this collaborative infrastructure was indirectly given by the Paediatric Committee of the EMA, when a priority list of off-patent products was established for which studies were required in children and adolescents. This list then served as the basis for the EU Seventh Framework Programme (FP7) community funding for research into off-patent medicines, object of its final call. Three projects were funded to examine the use and tolerability/safety of psychotropic medications in children and adolescents: (a) PERS (Paediatric European Risperidone Studies, www.pers-project.com), designed to assess the efficacy and long-term safety of risperidone in children and adolescents with conduct disorder and normal intellectual abilities (Glennon et al., 2014); (b) STOP (Suicidality: Treatment Occurring in Paediatrics, www.stop-study.com), assessing and monitoring medication-related suicidality in children and adolescents from three paediatric observational trials (risperidone and aripiprazole in conduct disorder; fluoxetine in depression, and montelukast in asthma); and (c) ADDUCE (Attention-Deficit Hyperactivity Disorder Drugs Use Chronic Effects, www.adhd-adduce.org) investigating the neurological, psychiatric, auxological and cardiovascular adverse effects of long-term methylphenidate administration in children and adults. Additional large-scale projects, also partially dealing with psychopharmacology while addressing major topics in child and adolescent psychopathology, were funded through FP7, namely: (a) TACTICS (The "Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes", http://www.tactics-project.eu/), which intends to establish predictive neural, genetic and molecular markers of compulsivity in paediatric populations, develop novel animal models to test pharmacological strategies against compulsivity, build translational biomarker databases and design future large-scale clinical trials accordingly; (b) AGGRESSOTYPE ("Aggression Subtyping for Improved Insight and Treatment Innovation in Psychiatric Disorders", http://www.aggressotype.eu/), (c) FEM-NAT CD ("Neurobiology and Treatment of Adolescent Female Conduct Disorder: The Central Role of Emotion Proces sing", http://www.femnat-cd.eu/), (d) MATRICS ("Multidisciplin ary Approaches to Translational Research In Conduct Syn dromes", http://matrics-project.eu/) and (e) ACTION ("Aggres sion in Children: unraveling gene-environment interplay to inform Treatment and InterventiON strategies", http://ec.europa.eu/research/health/medical-research/brain-research/projects/action_en.html) programs, each including nested pro jects aimed at identifying neural, (epi)genetic and molecular factors involved in the pathogenesis of aggression/antisocial behaviour, in order to develop and pilot-test symptomatic and preventive interventions in high-risk children with callous unemotional traits, and to identify innovative pharmacological interventions for conduct disorder. These large academic studies target a great deal of efficacy and tolerability/safety data, with evidence of true real-world effectiveness.

The Child and Adolescent Neuropsychopharmacology Network, supported by the ECNP, has been instrumental in building an infrastructure prompting several of the above-mentioned EU-funded projects. Additional centres have then teamed up into a partly overlapping Enpr-EMA European Child and Adolescent Clinical Psychopharmacology Network, which also received support from the European Network for Hyperkinetic Disorders (Eunethydis), a founding member of the Enpr-EMA network which continues to actively participate as a member of the coordinating committee. These centres have a solid track record in paediatric psychopharmacology, assuring adequate experimental design, patient recruitment, biomarker definition and clinical management in large-scale studies, including formal RCTs for the registration of innovative medications. The existence of this pan-European infrastructure ensures that the translation of neurobiological discoveries into much-needed pharmacological therapies will be pursued with the greatest reliability and rapidity. The pace of this process will also largely depend upon constructive legislation and regulations, improving economies, funding priorities, dissemination campaigns able to effectively inform patients and their families while counteracting ideological opposition towards psychopharmacological interventions in children and adolescents. The treatment of psychiatric disorders in youth and the prevention of their outburst in adolescents and adults represent two daunting, yet pivotal tasks, which well deserve every possible effort on everyone's part.

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Contributors

Antonio M. Persico took notes during the TNM meeting, outlined the paper's content, contributed to writing the paper's versions and collated sections provided by co-authors. Celso Arango and Jan K. Buitelaar chaired the TNM meeting and contributed to the writing of the paper. Christoph U. Correll, Benedetto Vitiello, Carmen Moreno, Alessandro Zuddas, Pieter J. Hoekstra, Jacob Vorstman, and Jeffrey C. Glennon were either presenters or discussants at the TNM meeting, shared notes and slides, and contributed to the writing of the paper. Two other members of the European Child and Adolescent Clinical Psychopharmacology Network, David Coghill and Ralf W. Dittmann, provided detailed comments. All authors approved the final draft of the manuscript.

Conflict of interest statement

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