Psychotropic Drug Prescription in Children and Adolescents: Approved Medications in European Countries and the United States

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Running title: Psychotropic medications' approval status

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Abstract

Objectives: The decision to prescribe a medication and the choice of which one are often complex, particularly in the field of child and adolescent psychiatry where evidence is scarce. The aim of this review is to provide a synthesis of psychotropic drugs approved in children and adolescents for psychiatric indications in several countries.

Methods: All psychopharmacological treatments used in child and adolescent psychiatry, approved by at least one regulatory agency from Switzerland, the United Kingdom, France, the European Union or the United States were considered. A comprehensive review of the summaries of product characteristics was performed.

Results: A total of 143 psychotropic drugs was included: 47 anxiolytics/hypnotics, 45 antidepressants, 37 antipsychotics, 10 medications for attention-deficit/hyperactivity disorder (ADHD) and 4 mood stabilizers. Only a few of these drugs were approved for use in children or adolescents (38%) at least for a single psychiatric diagnosis in at least one country. The therapeutic class with the lowest rate of approved status was antidepressants (20%), followed by mood stabilizers (25%), anxiolytics/hypnotics (28%), antipsychotics (57%) and medications for ADHD (100%). Important differences in approved diagnoses, ages and doses were observed between regulatory agencies. Tables presenting drugs for approved diagnoses based on age and regulatory agencies are presented in this paper. Drugs classified by regulatory agencies, with complete data on diagnoses, ages, doses, pharmaceutical forms and particular restrictions, are presented as electronic supplementary material.

Conclusion: This paper provides an overview to prescribers with respect to the approved medications in children and adolescents in selected European countries and the United States.

Keywords: Psychiatry; Children and adolescents; Psychotropic drugs; Approved indications; European countries; United States

Introduction

Prescription of psychotropic drugs in children and adolescents has increased globally in previous decades. This increase can be attributed to better accessibility of services, lower thresholds for diagnosis and treatment, availability of new generation medications, such as selective serotonin reuptake inhibitors and atypical antipsychotics, and pharmaceutical marketing (Thomas et al. 2006; Olfson et al. 2012; Meng et al. 2014; Halfdanarson et al. 2017; Kaguelidou et al. 2020).

Randomized controlled clinical trials are required to demonstrate the efficacy and safety of drugs before marketing authorization. On the basis of the conditions formally evaluated by the manufacturer, the regulatory authorities specify the therapeutic indications and the populations for which the drug is approved. These conditions are described in the summary of product characteristics (SmPC), also known as prescription drug labelling, written principally for health care professionals (Lal and Kremzner 2007).

Children and adolescents are generally not included in clinical trials during drug development. Consequently, relatively few medicines are approved in this population and considerable off-label prescription is used in clinical practice (Czaja and Valuck 2012). Off-label prescription, the use of a pharmaceutical drug outside the conditions specified in the product license, such as therapeutic indication, age, dose, pharmaceutical form and/or mode of administration (Haw and Stubbs 2007), is legal in many countries, contrary to public opinion, but the prescriber must carefully assess risk/benefit. The patient should be told the prescription is off-label and the information given meticulously documented. Due to the absence of examination by the regulatory authorities, off-label use is associated with potentially increased risk of toxicity and fewer established benefits. Furthermore, the costs to the health care system could be increased. Nevertheless, off-label prescription is sometimes the best solution and could provide a pathway for innovation in clinical practice (Radley et al. 2006). More approved indications are generally present with the old drugs compared to the new ones, due to less restrictive criteria some decades ago, and due to the time-lag in approving new agents.

In Switzerland, marketing authorizations of medicines are the responsibility of the Swiss Agency for Therapeutic Products, called Swissmedic (SM) (Swissmedic 2020). In the EU, the

European Medicines Agency (EMA) is responsible for the centralized authorization procedure, which results in a single marketing authorization that is valid in all EU countries. This procedure is compulsory for most innovative medicines, including medicines for rare diseases. The majority of medicines authorized in the EU, however, do not fall within the scope of the centralized procedure but are authorized by competent national authorities in the Member States. A marketing authorization can also be obtained simultaneously in several EU countries via the decentralized procedure for drugs that have not yet been authorized in any EU country or via the mutual-recognition procedure for drugs that are already authorized in one EU Member State (EMA 2016). In the United Kingdom authorization is made by the Medicines and Healthcare Products Regulatory Agency (MHRA) (MHRA 2020), and in France by the National Agency for the Safety of Medicines and Health Products (ANSM) (ANSM 2020). In the United States, the FDA gives drug approval (FDA 2020).

In the last decade, several articles have published brief tables of psychotropic drugs approved for children and adolescents, limited to antidepressants (Deng et al. 2018), antipsychotics (Caccia et al. 2011; Lee et al. 2018; Mathy and Malchair 2018; Zhu et al. 2018) or some classes of psychotropic drugs (Denizot et al. 2009; Kearns and Hawley 2014; Brauner et al. 2016; Nielsen et al. 2016; Putignano et al. 2019) in different countries: France (Denizot et al. 2009), Italy (Putignano et al. 2019), Denmark (Brauner et al. 2016; Nielsen et al. 2016), Belgium (Mathy and Malchair 2018), the United Kingdom (Caccia et al. 2011; Putignano et al. 2019), the United States (Kearns and Hawley 2014; Deng et al. 2018; Lee et al. 2018; Zhu et al. 2018; Putignano et al. 2019) and China (Deng et al. 2018; Zhu et al. 2018). Furthermore, most of these publications are out of date. In a recent publication, we reported approved indications for all psychotropic drugs in patients under age 18, but only in Switzerland and without dosing information (Ansermot et al. 2018). To the best of our knowledge, the present publication is the first that reports a comprehensive review of all psychotropic drugs approved in children and adolescents for psychiatric indications in several countries: Switzerland, the EU, the United Kingdom, France and the United States. Its aim is to provide an overview to prescribers with respect to the approved medications. This provides, equally and indirectly, knowledge concerning off-label prescription.

Method

Data sources and search strategy

Five therapeutic classes of drugs commonly prescribed in psychiatry in children and adolescents were considered: antidepressants, antipsychotics, anxiolytics/hypnotics, mood stabilizers and medicines for attention-deficit/hyperactivity disorder (ADHD) (Ansermot et al. 2018). Based on the World Health Organisation Collaborating Centre for Drug Statistics Methodology database (WHO 2020), which provides a complete list of internationally available medicines, all psychotropic drugs belonging to these classes were included. A thorough screening for official SmPC was performed for all these medicines in five databases of drug monitoring agencies: SM for Switzerland (Swissmedic 2020), the EMA for the EU (EMA 2020 ; European Commission 2020), the MHRA for the United Kingdom (MHRA 2020), the ANSM for France (ANSM 2020) and the FDA for the United States (FDA 2020). If no SmPC was available on the FDA website, while the status of the medicine was described as marketed, a complementary search was performed on the DailyMed website (DailyMed 2020).

When a SmPC for a drug was not found on one of these websites, meaning that no official evaluation has been performed in this country, the following information was noted in the results “not centrally authorized” for EMA and “not on the official site” for the other regulatory agencies. Medications without any SmPC available in any of the consulted databases were excluded from our research. When several SmPC were present on the same website for the same medicine, which was frequent for generic drugs, all monographs were read and taken into account because the information could vary between manufacturers. More than 1000 SmPC were reviewed in detail for this research.

Data selection

All parts of each SmPC were screened for information regarding psychiatric indications for children and adolescents. Indications in somatic medicine, neurology and anesthesiology, such as nocturnal enuresis for tricyclic antidepressants, epilepsy for mood stabilizers or premedication for benzodiazepines, were not included in our search. Each approved diagnosis was noted, as well as age categories (or weight), initial doses of the medication, need for divided dosing, progression of dosing, target doses for best therapeutic effects, maximum

authorized doses, different routes of administration and drug forms, particular restrictions (second intention or duration of treatment) and contraindications related to age of indication. The data were collected by an author (MS or AO) and verified independently by a second author (AO or NA).

Only the diagnoses formally approved for children and adolescents were considered as indications, but not those only suggested for use in this population. For example, oral lorazepam use in Switzerland has only a contraindication < 12 years, which could suggest an off-label use between 12-17 years. However, to be the most exhaustive possible, the suggested uses were pointed out. When the information available in the SmPC was not clear, the marketing authorization holders were contacted. The original terms used in the official SmPC were reported to describe the indications for each medicine. When, for the same drug in the same database, indications or dosages were different depending on the manufacturers, the differing indications and/or dose ranges were noted and the mention “indications/dosages depending on the SmPC” was added. If a medication had no psychiatric indication in a particular database for either adults or children/adolescents, the note “no psychiatric indication” was written if the drug had a psychiatric indication in at least one other database; otherwise, the drug was excluded. If a drug had a psychiatric indication for adults but not for children/adolescents, the note “no psychiatric indication < 18 years” was used if the drug had other indications (non-psychiatric) for children/adolescents. A medication was considered as contraindicated under a certain age (18 years or younger) if it was specified under the Contraindication section of the SmPC.

When a drug was not approved for children or adolescents, different notations were regularly observed in the SmPC to describe the status in this population, sometimes varying between different SmPC for the same drug on the same website or even inside the same SmPC. A subjective priority ranking was decided upon to assure reporting only the highest level term during data collection: “must not be used” > “only for adults” > “not indicated” > “not approved” > “should not be used” > “not recommended” > “not studied” > “not evaluated” > “not established” > “no data available”. If nothing was specified in the SmPC for children and adolescents, we noted “no information in the SmPC about < 18 years”. As the paper focuses

only on psychiatric treatment of children and adolescents, a possible absence of indication for adults was not reported in our results.

Results

A total of 143 different psychotropic drugs or combinations were reviewed in detail for indications in children and adolescents in the official drug databases of five regulatory agencies (SM, EMA, MHRA, ANSM and FDA): 45 antidepressants, 37 antipsychotics, 47 anxiolytics or hypnotics/sedatives, 4 mood stabilizers and 10 medications for ADHD. Complete information on these drugs is provided in Supplementary Tables S1-S5.

Among these medicines, only 54 (38%) are approved for use in patients under age 18 for at least one diagnosis in at least one database: 9 (20%) antidepressants, 21 (57%) antipsychotics, 13 (28%) anxiolytics or hypnotics/sedatives, 1 (25%) mood stabilizer and 10 (100%) medications for ADHD; see Tables 1-5.

For the treatment of major depressive disorders, 4 antidepressants are approved: amitriptyline (MHRA ≥ 16 years, ANSM < 18 years), nortriptyline (MHRA in adolescents), escitalopram (FDA ≥ 12 years) and fluoxetine (MHRA, ANSM and FDA ≥ 8 years); see Table 1. Lithium is approved in combination with antidepressants for resistant depression (SM ≥ 12 years); see Table 4.

For obsessive-compulsive disorders, 4 antidepressants are indicated: clomipramine (SM, ANSM and FDA ≥ 10 years), fluoxetine (FDA ≥ 7 years), fluvoxamine (SM, MHRA, ANSM and FDA ≥ 8 years) and sertraline (SM, MHRA, ANSM and FDA ≥ 6 years); see Table 1.

Fourteen antipsychotics are indicated for schizophrenia and/or psychotic disorders: chlorpromazine (MHRA ≥ 1 year), haloperidol (SM, MHRA and ANSM ≥ 13 years, FDA ≥ 3 years), loxapine (ANSM ≥ 15 years), pimozide (MHRA ≥ 12 years), prochlorperazine (FDA ≥ 2 years), promazine (SM ≥ 12 years), thioridazine (FDA < 18 years), trifluoperazine (MHRA and FDA ≥ 6 years), aripiprazole (SM and FDA ≥ 13 years, EMA, MHRA and ANSM ≥ 15 years), lurasidone (EMA and FDA ≥ 13 years), olanzapine (FDA ≥ 13 years), paliperidone (EMA ≥ 15 years, FDA ≥ 12 years), quetiapine (SM and FDA ≥ 13 years) and risperidone (FDA ≥ 13 years); see Table 2.

For the treatment of manic and/or mixed episodes in bipolar disorders, 5 antipsychotics are approved: aripiprazole (SM, EMA, MHRA and ANSM ≥ 13 years, FDA ≥ 10 years), asenapine (FDA ≥ 10 years), olanzapine (FDA ≥ 13 years), quetiapine (SM and FDA ≥ 10 years) and risperidone (SM ≥ 15 years, FDA ≥ 10 years); see Table 2. Among the mood stabilizers, only lithium is approved for the acute phase and maintenance in bipolar disorders (SM ≥ 12 years, FDA ≥ 7 years); see Table 4. For the treatment of depressive episodes in bipolar I disorder, the fluoxetine/olanzapine combination (FDA ≥ 10 years) and lurasidone (FDA ≥ 10 years) are approved (Tables 1 and 2).

Eight antipsychotics have an indication for agitation or behavioral problems not specified or associated with psychotic disorders: chlorpromazine (ANSM ≥ 3 years, FDA ≥ 6 months), cyamemazine (ANSM ≥ 3 years), haloperidol (FDA ≥ 3 years), levomepromazine (MHRA < 18 years, ANSM ≥ 3 years), loxapine (ANSM ≥ 15 years), pipamperone (ANSM ≥ 5 years), trifluoperazine (MHRA ≥ 3 years) and zuclopenthixol (ANSM in children); see Table 2. Six antipsychotics also have a more precise indication for behavioral problems in autism or intellectual disability, but are not necessarily all exclusive to this type of population: chlorpromazine (MHRA ≥ 1 year), haloperidol (SM, MHRA and ANSM ≥ 6 years), pimozide (ANSM ≥ 6 years), sulpiride (ANSM ≥ 6 years), aripiprazole (FDA ≥ 6 years) and risperidone (SM, MHRA, ANSM and FDA ≥ 5 years). Some benzodiazepines also have an indication for agitation: diazepam (SM ≥ 6 months, MHRA ≥ 1 year) and prazepam (SM ≥ 3 years); see Table 3. Lithium is also approved for the treatment of severe chronic aggressiveness (SM ≥ 12 years); see Table 4.

Eight drugs are indicated for treating anxiety: bromazepam (SM < 18 years), chlordiazepoxide (FDA ≥ 6 years), clobazam (SM ≥ 3 years), clorazepate (SM ≥ 9 years, ANSM ≥ 6 years), diazepam (SM and FDA ≥ 6 months, MHRA ≥ 1 year, ANSM ≥ 6 years), prazepam (SM ≥ 3 years, ANSM ≥ 12 years), hydroxyzine (FDA < 18 years) and meprobamate (FDA ≥ 6 years); see Table 3. Among the antidepressants, only duloxetine (FDA ≥ 7 years) is approved for generalized anxiety disorder (Table 1).

For the treatment of sleep disorders and insomnia, 5 drugs are approved: hydroxyzine (ANSM ≥ 3 years), diphenhydramine (SM ≥ 2 years and MHRA ≥ 16 years), doxylamine (SM and FDA ≥ 12 years), chloral hydrate (SM < 18 years, MHRA ≥ 2 years) and pentobarbital (FDA < 18

years); see Table 3. Melatonin is approved specifically in children and adolescents for insomnia in autism spectrum disorders or Smith-Magenis syndrome (SM and EMA ≥ 2 years) and for insomnia in ADHD (MHRA ≥ 6 years). The only indicated medicine for the treatment of night terrors and somnambulism is diazepam (MHRA < 18 years).

To treat tics or Tourette disorder, 4 antipsychotics are approved: haloperidol (SM, MHRA and ANSM ≥ 10 years, FDA ≥ 3 years), pimozide (ANSM ≥ 6 years, FDA ≥ 12 years), tiapride (SM ≥ 7 years, ANSM ≥ 6 years) and aripiprazole (FDA ≥ 6 years); see Table 2.

The drugs indicated for the treatment of ADHD are dexmethylphenidate (SM and FDA ≥ 6 years), methylphenidate (SM, MHRA, ANSM and FDA ≥ 6 years), amphetamine (FDA ≥ 6 years), dexamfetamine (MHRA ≥ 6 years), lisdexamfetamine (SM, MHRA and FDA ≥ 6 years), methamphetamine (FDA ≥ 6 years), a combination of amphetamine mixed salts with dextroamphetamine mixed salts (FDA ≥ 6 years), atomoxetine (SM, MHRA and FDA ≥ 6 years), clonidine (FDA ≥ 6 years) and guanfacine (SM, EMA and FDA ≥ 6 years); see Table 5.

Discussion

In the present work, all psychotropic drugs from the main therapeutic classes registered in at least one database of the five regulatory agencies in Europe and the United States were reviewed in detail for psychiatric indications in children and adolescents. Our results show that only 33% of the available medicines are officially approved in children (6 months-11 years) for at least one psychiatric indication in at least one country and this slightly increases to 38% in adolescents (12-17 years).

The decision to prescribe a drug and the choice of drug are often complex; risk/benefit should be carefully evaluated, particularly in children and adolescents. This paper seeks to provide an overview to prescribers with respect to the approved medications. More than 20 diagnoses commonly observed in children and adolescents have at least one medicine approved by at least one regulatory agency. The choice of a psychopharmacological treatment should preferably fall among drugs which already have an indication for children or adolescents in the prescriber's country. When no drugs are approved for a particular diagnosis in the prescriber's country, authorization in another country could represent an indication to prescribe it.

Nevertheless, some approved drugs may no longer be recommended for best clinical practice, particularly the medications used for several decades. Thus, the choice of the drug should also be based primarily on the most recent national or international treatment guidelines or expert opinions. Many treatment guidelines are regularly published and updated; they will not be presented and discussed here, as it is outside the scope of this paper. However, to illustrate the problematic gap between the official indications and current treatment guidelines, the pharmacological treatment of major depressive disorders will be discussed.

In Switzerland, for example, no antidepressant is approved for the treatment of major depressive disorders. If an antidepressant is required for a patient, the prescriber should choose a medication that is approved in another country, such as fluoxetine (MHRA, ANSM and FDA ≥ 8 years) or escitalopram (FDA ≥ 12 years). The National Institute for Health and Care Excellence (NICE) guideline recommends using fluoxetine as the first-line pharmacological treatment of depression in children and adolescents, and to use sertraline or citalopram as second-line (NICE 2019). Sertraline and citalopram are approved for the treatment of depression in adults, but not in children and adolescents. Sertraline is approved for the treatment of obsessive-compulsive disorders in children ≥ 6 years (SM, MHRA, ANSM and FDA), which is not the case for citalopram. In the meta-analysis of Cochrane, there was a statistically significant reduction in depressive symptoms with fluoxetine, escitalopram and sertraline, compared with placebo, but a statistically significant increase in the remission rate was observed only with fluoxetine (Hetrick et al. 2012). In the meta-analysis of Cipriani et al., fluoxetine, escitalopram and sertraline were statistically more effective than placebo in the pairwise analyses, but in the network analyses, only fluoxetine was statistically significantly more effective (Cipriani et al. 2016). Despite some tricyclic antidepressants still being approved by some authorities in children and adolescents for historical reasons, they should no longer be used for the treatment of depression in this population (NICE 2019), because they have not been shown to be effective and are less tolerated than selective serotonin reuptake inhibitors (Weller and Weller 2000; Hazell and Mirzaie 2013).

The therapeutic class with the lowest rate of approved status in child and adolescent psychiatry is antidepressants (20%), which are mainly indicated for major depressive disorder (only 9%) and obsessive-compulsive disorders (only 9%). This low rate is probably due to the

increased risk of suicide-related behavior (suicidal thoughts and suicide attempt) and hostility (predominantly aggression, oppositional behavior and anger) observed in clinical studies in young patients (Hammad et al. 2006; Hetrick et al. 2012; Cipriani et al. 2016). A black box warning about the emergence of suicidal behavior has been included in the drug labelling of all antidepressants since 2004. This warning has to be taken into account and informed about, particularly when an off-label antidepressant is prescribed. Only 28% of the anxiolytics/hypnotics have an indication for children and adolescents, mainly anxiety (17%) or sleep disorders (13%), but also agitation or excitation for some of them (6%). Among the mood stabilizers, only lithium is authorized in child and adolescent psychiatry. Antipsychotics have a higher level of approval (57%), and are mainly indicated for schizophrenia or psychotic disorders (38%), followed by agitation or behavioral problems not specified or present in psychotic disorders, autism or intellectual disability (32%), manic or mixed episodes in bipolar disorders (14%) and tics (11%). The highest approval rate is for medications for ADHD (100%), a pathology that typically starts during childhood.

The low proportion of approved medications in children and adolescents, linked to the limited number of clinical trials conducted during drug development, occurs for multiple reasons: (1) ethical and legal considerations concerning protection of vulnerable populations; (2) difficulties in obtaining informed consent for underage patients; (3) developmental concerns; (4) necessity of considering each age category separately (neonates, infants, children, adolescents); (5) blood sampling or other painful medical examinations during clinical trials; (6) difficulties in developing formulations appropriate for children; (7) small sample sizes compared to the adult population; (8) expense and (9) low financial incentives for the pharmaceutical companies due to low numbers of potentially treated patients (Cuzzolin et al. 2003; Czaja and Valuck 2012; Tanemura et al. 2019). Different regulations have been introduced by the authorities to provide incentives for the manufacturers to initiate new clinical trials in children and adolescents, such as the Food and Drug Administration (FDA) Modernization Act, the Best Pharmaceuticals for Children Act and The Pediatric Research Equity Act in the United States (Bourgeois and Hwang 2017), or the Paediatric Investigation Plan in the European Union (EU) (EMA 2021). The lack of authorization for children and adolescents does not necessarily mean that the medication is inappropriate or that there is a

lack of evidence. It only means that the evidence of efficacy and safety necessary for inclusion in the label has not been submitted or approved by the regulatory authorities. There may be data from non-randomized controlled clinical trials supporting possible effectiveness, or the manufacturer may choose not to apply for new labelling despite sufficient evidence (Cuzzolin et al. 2003; Czaja and Valuck 2012; Putignano et al. 2019). In the United States, the law allows some unapproved drugs to be marketed if they meet the criteria of generally recognized as safe and effective or grandfathered (FDA 2021).

The regulatory agency with the highest number of psychotropic drugs with at least one SmPC available in its database (with or without indications in patients < 18 years) is the FDA (n=103), followed by SM (n=84), MHRA (n=77), ANSM (n=75) and EMA (n=21). The low number of SmPC available for EMA is explained by the fact that only a few psychotropic drugs have been approved via the centralized procedure, which was not possible before 1995 (EMA 2016). When only psychiatric indications in patients under 18 years are considered, the regulatory agency that approved the most drugs and diagnoses, respectively, is the FDA (n=36 and 50), followed by SM (n=24 and 36), ANSM (n=22 and 29), MHRA (n=20 and 32), and EMA (n=5 and 6). Important differences in the official drug monographs among the various drug agencies are also observed concerning the type of approved diagnoses, ages and doses.

The minimum age authorized for use of these drugs varies based on the pathology being treated, for example: 3-6 years for severe behavioral problems (even 6 months for chlorpromazine), 3-12 years for anxiety (even 6 months for diazepam), 2-16 years for sleep disorders, 6 years for ADHD treatments, 6-10 years for obsessive-compulsive disorders, 6-12 years for tics, 7-12 years for lithium treatment, 8-16 years for major depressive disorders, 10-15 years for manic episodes in bipolar disorders, and 12-15 years for schizophrenia (even less for some old antipsychotics). Very low ages are approved for some drugs used for several decades, chlorpromazine for schizophrenia (MHRA ≥ 1 year), for example, which is not the case with newer drugs. Prescribers should be cautious about using these old drugs in young children, as the approval criteria might have been less restrictive in the past. For some other old drugs, the approved ages are not clear, for example for thioridazine for schizophrenia (FDA < 18 years) or nortriptyline for major depressive disorder (MHRA in adolescents).

The low rate of psychotropic medications approved in underage patients observed in our review, especially for certain therapeutic classes, is in line with the high rate of off-label prescriptions observed in this population. In adolescents hospitalized in a Swiss psychiatric university hospital, the prevalence of off-label psychotropic drug prescriptions was 68% in 2014 (Ansermot et al. 2018). In Germany, using claims data, the annual share of off-label prescription in 2011 was 36% for antidepressants (Schroder et al. 2017a) and 62% for antipsychotics (Schroder et al. 2017b). Antipsychotics were mainly prescribed to manage aggressive and impulsive behaviors, which raises concerns, since the efficacy and safety of these drugs have not been sufficiently investigated in these indications (Schroder et al. 2017b). In a cross-sectional study in Denmark, 32% of psychopharmacological prescriptions were off-label in a child and adolescent psychiatric setting in 2014 (Brauner et al. 2016). In the United States, a cross-sectional study in ambulatory care settings found that 91% of antidepressants prescribed for children and adolescents were off-label from 2000 to 2006 (Lee et al. 2012). A systematic review of prescription trends showed that between 36-93% of antipsychotics were prescribed off-label in children and adolescents (Carton et al. 2015). These high rates of off-label prescription use highlight the need for additional clinical studies in children and adolescents to evaluate the safety and clinical efficacy of these drugs.

An important part of this work was to carefully standardize the information that is often presented differently among SmPC, particularly for old drugs, without modifying its accuracy. Differences among SmPC from different manufacturers for the same drug in the same database were also observed. In addition, some discrepancies between different parts of a single SmPC were also observed for some drugs. For example, some tricyclic antidepressants were not approved for patients under age 18 in the FDA labels, but were suggested for use for adolescents under the Dosage and Administration section. When the approved indications, ages or dosages were not clear, the marketing authorization holders were contacted to obtain more precise information. However, in most cases, the manufacturers referred only to the SmPC without additional information.

Limitations

The first limitation of this work is that SmPC from only five regulatory agencies were reviewed, namely, those of Switzerland, France, the United Kingdom, the EU and the United States. Prescribers from other countries should first consider drugs and official information approved in their own country. However, when no drug is indicated for a particular diagnosis, or when the approved drugs are not suitable for a particular patient, the present paper can help prescribers choose a drug based on the approval status in other countries. The second limitation is that the recommendations certified by national and international drug monitoring authorities are regularly evolving; new studies could be performed with new data on efficacy or toxicity, which could change the approved diagnoses, ages or doses. New drugs with potential indications in children and adolescents will also probably be marketed in the future. The third limitation is that despite every effort being made to ensure the accuracy of this information, an error, inaccuracy or misinterpretation of the official data cannot be totally excluded, particularly for some drugs where the approved diagnoses, ages or doses were not clearly formulated in the SmPC. The authors decline any responsibility for use of the information provided in this paper. Prescribers must always refer to current information on official websites.

Conclusion

Our review shows that only a few psychotropic medications are officially approved for use in children or adolescents for a psychiatric indication, particularly for some therapeutic classes such as antidepressants, which is in line with the high rate of off-label prescriptions observed in this population. Significant differences are observed among the various regulatory agencies concerning approved diagnoses, ages and doses. These results highlight the need for additional clinical studies in children and adolescents to evaluate the safety and efficacy of these drugs.

Clinical Significance

This paper provides an overview for prescribers with respect to the approved psychotropic medications in children and adolescents for psychiatric indications in several countries. The

choice of a psychopharmacological treatment should preferably fall among medications which already have an indication for children or adolescents in the prescriber's country. When no drugs are approved for a particular diagnosis, the present paper can help prescribers choose a drug based on the approval status in other countries. However, the approved drugs are not necessarily the best treatments, particularly those used for several decades. The most recent clinical practice guidelines should be considered before a drug is prescribed.

Supplementary Material

Supplementary Table S1

Supplementary Table S2

Supplementary Table S3

Supplementary Table S4

Supplementary Table S5

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Table 1. Antidepressants approved in children and adolescents for psychiatric indications.

Drug	Major depressive disorders	Obsessive-compulsive disorders	Other
Tricyclic antidepressants			
amitriptyline	≥ 16 years (MHRA) < 18 years (ANSM)		
clomipramine		≥ 10 years (SM, ANSM, FDA)	
nortriptyline	In adolescents (MHRA)		
Selective serotonin reuptake inhibitors			
escitalopram	≥ 12 years (FDA)		
fluoxetine	≥ 8 years (MHRA, ANSM, FDA)	≥ 7 years (FDA)	
fluoxetine + olanzapine			Depressive episodes in bipolar I disorder ≥ 10 years (FDA)
fluvoxamine		≥ 8 years (SM, MHRA, ANSM, FDA)	
sertraline		≥ 6 years (SM, MHRA, ANSM, FDA)	
Serotonin and norepinephrine reuptake inhibitor			
duloxetine			Generalized anxiety disorder ≥ 7 years (FDA)

For detailed information, including doses, see Table S1 in the electronic supplementary material. If the formulation is not specified in the table, the indications correspond to an oral form only. SM: Swissmedic; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration.

Table 2. Antipsychotics approved in children and adolescents for psychiatric indications.

Drug	Schizophrenia and/or psychotic disorders	Manic and/or mixed episodes in bipolar disorders	Agitation and/or behavioral problems including in autism and intellectual disability	Other
Typical antipsychotics				
chlorpromazine	≥ 1 year oral/inj (MHRA)		≥ 1 year oral/inj (MHRA[a]) ≥ 3 years (ANSM) ≥ 6 months oral/inj (FDA)	
cyamemazine			≥ 3 years (ANSM)	
haloperidol	≥ 13 years (SM, MHRA, ANSM) ≥ 3 years (FDA)		≥ 6 years (SM[a], MHRA[a], ANSM[a]) ≥ 3 years (FDA)	Tics ≥ 10 years (SM, MHRA, ANSM), ≥ 3 years (FDA)
levomepromazine			< 18 years (MHRA) ≥ 3 years (ANSM)	
loxapine	≥ 15 years (ANSM)		≥ 15 years inj (ANSM)	
pimozide	≥ 12 years (MHRA)		≥ 6 years (ANSM[a])	Tics ≥ 6 years (ANSM), ≥ 12 years (FDA)
pipamperone			≥ 5 years (ANSM)	
prochlorperazine	≥ 2 years oral/inj (FDA)			
promazine	≥ 12 years (SM)			
sulpiride			≥ 6 years (ANSM[a])	
thioridazine	< 18 years (FDA)			
tiapride				Tics ≥ 7 years (SM), ≥ 6 years (ANSM)
trifluoperazine	≥ 6 years (MHRA, FDA)		≥ 3 years (MHRA)	
zuclopenthixol			In children depot (ANSM)	
Atypical antipsychotics				
aripiprazole	≥ 13 years (SM, FDA) ≥ 15 years (EMA, MHRA, ANSM)	≥ 13 years (SM, EMA, MHRA, ANSM) ≥ 10 years (FDA)	≥ 6 years (FDA[a])	Tourette disorder ≥ 6 years (FDA)
asenapine		≥ 10 years (FDA)		
lurasidone	≥ 13 years (EMA, FDA)			Depressive episodes in bipolar I disorder ≥ 10 years (FDA)
olanzapine	≥ 13 years (FDA)	≥ 13 years (FDA)		

Table 2. Continued.

Drug	Schizophrenia and/or psychotic disorders	Manic and/or mixed episodes in bipolar disorders	Agitation and/or behavioral problems including in autism and intellectual disability	Other
paliperidone	≥ 15 years (EMA) ≥ 12 years (FDA)			
quetiapine	≥ 13 years (SM, FDA)	≥ 10 years (SM, FDA)		
risperidone	≥ 13 years (FDA)	≥ 15 years (SM) ≥ 10 years (FDA)	≥ 5 years (SM[a], MHRA[a], ANSM[a], FDA[a])	

For detailed information, including doses, see Table S2 in the electronic supplementary material. If the formulation is not specified in the table, the indications correspond to an oral form only. SM: Swissmedic; EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration; inj: short-acting injection; depot: long-acting injection. [a]These drugs are approved in autism and/or intellectual disability, but are not necessarily all exclusive to this type of population.

Table 3. Anxiolytics and hypnotics/sedatives approved in children and adolescents for psychiatric indications.

Drug	Anxiety	Sleep disorders and/or insomnia	Other
Benzodiazepine anxiolytics			
bromazepam	< 18 years (SM)		
chlordiazepoxide	≥ 6 years (FDA)		
clobazam	≥ 3 years (SM)		
clorazepate	≥ 9 years (SM) ≥ 6 years (ANSM)		Alcohol withdrawal ≥ 6 years (ANSM)
diazepam	≥ 6 months oral/inj (SM) ≥ 1 year rectal (MHRA) ≥ 6 years (ANSM) ≥ 6 months (FDA)		Agitation ≥ 6 months oral/inj (SM), ≥ 1 year rectal (MHRA) Alcohol withdrawal ≥ 6 months oral/inj (SM), ≥ 6 years (ANSM), ≥ 6 months (FDA) Night terrors / Somnambulism < 18 years (MHRA)
prazepam	≥ 3 years (SM) ≥ 12 years (ANSM)		Agitation ≥ 3 years (SM)
Other anxiolytics			
hydroxyzine	< 18 years (FDA)	≥ 3 years (ANSM)	
meprobamate	≥ 6 years (FDA)		
Other hypnotics/sedatives			
chloral hydrate		< 18 years (SM) ≥ 2 years (MHRA)	Excitation < 18 years (SM)
diphenhydramine		≥ 2 years (SM) ≥ 16 years (MHRA)	
doxylamine		≥ 12 years (SM, FDA)	
melatonin		In autism spectrum disorders or Smith-Magenis syndrome ≥ 2 years (SM, EMA) In ADHD ≥ 6 years (MHRA)	
pentobarbital		< 18 years inj (FDA)	

For detailed information, including doses, see Table S3 in the electronic supplementary material. If the formulation is not specified in the table, the indications correspond to an oral form only. SM: Swissmedic; EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration; inj: short-acting injection; ADHD: attention-deficit/hyperactivity disorder.

Table 4. Mood stabilizers approved in children and adolescents for psychiatric indications.

Drug	Acute phase and prophylaxis of bipolar disorders	Combination with antidepressants for resistant depression	Severe chronic aggressiveness
lithium	≥ 12 years (SM) ≥ 7 years (FDA)	≥ 12 years (SM)	≥ 12 years (SM)

For detailed information, including doses, see Table S4 in the electronic supplementary material. If the formulation is not specified in the table, the indications correspond to an oral form only. SM: Swissmedic; FDA: Food and Drug Administration.

Table 5. Medications for attention-deficit/hyperactivity disorder approved in children and adolescents for psychiatric indications.

Drug	Attention deficit hyperactivity disorder	Refractory hyperkinetic states
Non-amphetamine psychostimulants		
dexmethylphenidate	≥ 6 years (SM, FDA)	
methylphenidate	≥ 6 years (SM, MHRA, ANSM) ≥ 6 years oral/transdermal (FDA)	
Amphetamine psychostimulants		
amphetamine	≥ 6 years (FDA)	
amphetamine mixed salts + dextroamphetamine mixed salts	≥ 6 years (FDA)	
dexamfetamine	≥ 6 years (MHRA)	≥ 3 years (MHRA)
lisdexamfetamine	≥ 6 years (SM, MHRA, FDA)	
methamphetamine	≥ 6 years (FDA)	
Non-psychostimulants		
atomoxetine	≥ 6 years (SM, MHRA, FDA)	
clonidine	≥ 6 years (FDA)	
guanfacine	≥ 6 years (SM, EMA, FDA)	

For detailed information, including doses, see Table S5 in the electronic supplementary material. If the formulation is not specified in the table, the indications correspond to an oral form only. SM: Swissmedic; EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration.

Table S1. Antidepressants' approval status in children and adolescents for psychiatric indications

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
Tricyclic antidepressants			
amitriptyline (SER, NE multimodal)	Must not be used < 18 years	*Not centrally authorized (EMA)* **Major depressive disorders ≥ 16 years** (MHRA) Start 30-75 mg/d, maintenance dose 50-100 mg/d (lower dose may be satisfactory), dosage depending on the SmPC Should not be used < 18 years depending on the SmPC **Major depressive disorders < 18 years** (ANSM) Dosage ≤ 1 mg/kg/d No psychiatric indication < 18 years depending on the SmPC	Not approved < 18 years (but not recommended < 12 years and suggested for use in adolescents for major depressive disorders at 50 mg/d with divided intakes under Dosage and Administration section)
amitriptyline + chlordiazepoxide (SER, NE multimodal + GABA PAM)	Not recommended < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not approved < 18 years
amitriptyline + perphenazine (SER, NE multimodal + DA antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years (but suggested for use in adolescents for depression associated with anxiety at 10 mg amitriptyline with 4 mg perphenazine 3-4 times daily under Dosage and Administration section)
amoxapine (NE, SER reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* No information in the SmPC about < 18 years (ANSM)	Not approved < 18 years
clomipramine (SER, NE reuptake inhibitor)	**Obsessive-compulsive disorders ≥ 10 years** Start 25 mg/d, max 3 mg/kg/d, but no more than 100 mg/d the first 2 weeks and then no more than 200 mg/d	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) **Obsessive-compulsive disorders ≥ 10 years** (ANSM) Start 25 mg/d, max 3 mg/kg/d, but no more than 100 mg/d the first 2 weeks and then no more than 200 mg/d	**Obsessive-compulsive disorders ≥ 10 years** Start 25 mg/d, max 3 mg/kg/d, but no more than 100 mg/d the first 2 weeks and then no more than 200 mg/d

Table S1. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
desipramine (NE reuptake inhibitor)	*Not on the official site*	Not centrally authorized for psychiatric indication (EMA) *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not approved < 18 years (but suggested for use in adolescents for major depressive disorders at initial dose of 25 mg/d and max dose of 150 mg/d under Dosage and Administration section)
dosulepin (SER, NE reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) No information in the SmPC about < 18 years (ANSM)	*Not on the official site*
doxepin (NE, SER multimodal)	*Not on the official site*	*Not centrally authorized (EMA)* Not recommended < 12 years for major depressive disorders (MHRA) Pediatric doses not specified No data available < 18 years (ANSM)	Not approved < 18 years (but not recommended < 12 years for major depressive disorders under Indications section for some SmPC)
imipramine (SER, NE reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* No psychiatric indication < 18 years (MHRA) No psychiatric indication < 18 years (ANSM)	Not approved < 18 years (but suggested for use in adolescents for major depressive disorders at an initial dose of 30-40 mg/d and a max dose of 100 mg/d under Dosage and Administration section)
lofepramine (NE, SER reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) *Not on the official site (ANSM)*	*Not on the official site*
melitracen + flupentixol (NC + DA, SER antagonist)	Must not be used < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*
nortriptyline (NE reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* **Major depressive disorders in adolescents** (MHRA) 30-50 mg/d in divided doses Should not be used < 18 years depending on the SmPC *Not on the official site (ANSM)*	Not approved < 18 years (but suggested for use in adolescents for major depressive disorders at 30-50 mg/d under Dosage and Administration section)

Table S1. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
opipramol (NC)	Must not be used < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*
protriptyline (NE reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not approved < 18 years (but suggested for use in adolescents for symptoms of mental depression at 5 mg 3 times daily under Dosage and Administration section)
trimipramine (SER, DA antagonist)	Should not be used < 18 years	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) Not recommended < 18 years (ANSM)	Not approved < 18 years (but suggested for use in adolescents for major depressive disorders at an initial dose of 50 mg/d and a max dose of 100 mg/d under Dosage and Administration section) (DailyMed)
Tetracyclic antidepressants			
maprotiline (NE reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* Not recommended < 18 years (ANSM)	Not approved < 18 years
mianserin (NE multimodal)	Not recommended < 18 years	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) Not recommended < 18 years (ANSM)	*Not on the official site*
mirtazapine (NE, SER multimodal)	Must not be used < 18 years	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) Should not be used < 18 years (ANSM)	Not approved < 18 years
Monoamine oxidase inhibitors			
iproniazid (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* No data available < 18 years (ANSM)	*Not on the official site*
isocarboxazid (SER, NE, DA enzyme inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* Not indicated < 18 years (MHRA) *Not on the official site (ANSM)*	Not approved < 18 years (but not recommended < 16 years for major depressive disorders under Precaution section)

Table S1. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
moclobemide (SER, NE, DA enzyme inhibitor)	Contraindicated < 18 years	*Not centrally authorized (EMA)* Contraindicated < 18 years (MHRA) No data available < 18 years, contraindicated < 15 years (ANSM)	*Not on the official site*
phenelzine (SER, NE, DA enzyme inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* Not indicated < 16 years for atypical depression (MHRA) Pediatric doses not specified *Not on the official site (ANSM)*	Not approved < 18 years
tranylcypromine (SER, NE, DA multimodal)	*Not on the official site*	*Not centrally authorized (EMA)* Not indicated < 18 years (MHRA) *Not on the official site (ANSM)*	Not approved < 18 years
Selective serotonin reuptake inhibitors			
citalopram (SER reuptake inhibitor)	Must not be used < 18 years	*Not centrally authorized (EMA)* Must not be used < 18 years (MHRA) Must not be used < 18 years (ANSM)	Not approved < 18 years
escitalopram (SER reuptake inhibitor)	Must not be used < 18 years	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) Must not be used < 18 years (ANSM)	**Major depressive disorders ≥ 12 years** Start 10 mg/d, 10 mg/d recommended, increase to max 20 mg/d after min 3 weeks if needed

Table S1. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
fluoxetine (SER reuptake inhibitor)	Not recommended < 18 years	*Not centrally authorized (EMA)* **Major depressive disorders ≥ 8 years** (MHRA and ANSM) If depression is unresponsive to psychological therapy after 4-6 sessions, start 10 mg/d, increase to 20 mg/d after 1-2 weeks if needed, max 20 mg/d, consider lower doses for lower weight children Not indicated < 18 years depending on the SmPC of MHRA	**Major depressive disorders ≥ 8 years** Lower weight children: start 10 mg/d, increase to 20 mg/d after several weeks if needed, max 20 mg/d Higher weight children: start 10-20 mg/d, after 1 week at 10 mg/d increase to 20 mg/d, max 20 mg/d **Obsessive-compulsive disorders ≥ 7 years** Lower weight children: start 10 mg/d, increase after several weeks if needed, 20-30 mg/d recommended Higher weight children: start 10 mg/d, increase to 20 mg/d after 2 weeks, increase again after several weeks if needed, 20-60 mg/d recommended
fluoxetine + olanzapine (SER reuptake inhibitor + DA, SER antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**Depressive episodes in bipolar I disorder ≥ 10 years** Start 25 mg/d fluoxetine with 3 mg/d olanzapine (or 20 mg / 2.5 mg if the marketed combination is not used), max 50 mg/d fluoxetine with 12 mg/d olanzapine
fluvoxamine (SER reuptake inhibitor)	**Obsessive-compulsive disorders ≥ 8 years** Start 25 mg/d, increase by 25 mg/d per week if needed, if > 50 mg/d divide in two intakes, max 150 mg/d (8-12 years) or max 200 mg/d (13-17 years)	*Not centrally authorized (EMA)* **Obsessive-compulsive disorders ≥ 8 years** (MHRA and ANSM) Start 25 mg/d, increase by 25 mg/d every 4-7 days if needed, if > 50 mg/d divide in two intakes, max 200 mg/d	**Obsessive-compulsive disorders ≥ 8 years** Start 25 mg/d, increase by 25 mg/d every 4-7 days if needed, if > 50 mg/d divide in two intakes, max 200 mg/d (8-11 years) or max 300 mg/d (12-17 years)
paroxetine (SER reuptake inhibitor)	Must not be used < 18 years	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) Not recommended < 18 years (ANSM)	Not approved < 18 years

Table S1. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
sertraline (SER reuptake inhibitor)	**Obsessive-compulsive disorders ≥ 6 years** Start 25 mg/d, increase by 25 mg/d after 1 week (6-12 years), or start 50 mg/d (13-17 years), increase by 50 mg/d per week if needed, max 200 mg/d (take into consideration the lower weight of children)	*Not centrally authorized (EMA)* **Obsessive-compulsive disorders ≥ 6 years** (MHRA and ANSM) Start 25 mg/d, increase by 25 mg/d after 1 week if needed (6-12 years), or start 50 mg/d (13-17 years), increase by 50 mg/d per week if needed, max 200 mg/d (take into consideration the lower weight of children)	**Obsessive-compulsive disorders ≥ 6 years** Start 25 mg/d (6-12 years) or 50 mg/d (13-17 years), increase by 25-50 mg/d per week if needed, max 200 mg/d (take into consideration the lower weight of children)
Serotonin and norepinephrine reuptake inhibitors			
desvenlafaxine (SER, NE reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not approved < 18 years
duloxetine (SER, NE reuptake inhibitor)	Not indicated < 18 years	Should not be used < 18 years (EMA) Should not be used < 18 years (MHRA) Must not be used < 18 years (ANSM)	**Generalized anxiety disorder ≥ 7 years** Start 30 mg/d, increase to 60 mg/d after 2 weeks if needed, 30-60 mg/d recommended, max 120 mg/d Not approved < 18 years depending on the SmPC
levomilnacipran (NE, SER reuptake inhibitor)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not approved < 18 years
milnacipran (NC)	*Not on the official site*	Not centrally authorized for psychiatric indication (EMA) *Not on the official site (MHRA)* Not recommended < 18 years (ANSM)	No psychiatric indication
venlafaxine (SER, NE reuptake inhibitor)	Contraindicated < 18 years	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) Not recommended < 18 years (ANSM)	Not approved < 18 years

Table S1. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
Other antidepressants			
agomelatine (melatonin, SER agonist, antagonist)	Must not be used < 18 years	Not recommended < 18 years (EMA) Not recommended < 18 years (MHRA) Not recommended < 18 years (ANSM)	*Not on the official site*
bupropion (NE, DA reuptake inhibitor, releaser)	Not indicated < 18 years	Not centrally authorized for psychiatric indication (EMA) Not recommended < 18 years (MHRA) Not recommended < 18 years (ANSM)	Not established < 18 years
esketamine nasal (glutamate antagonist)	Not indicated < 18 years	Not studied < 18 years (EMA) Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	Not approved < 18 years
L-tryptophan (NC)	*Not on the official site*	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) *Not on the official site (ANSM)*	*Not on the official site*
nefazodone (SER antagonist, agonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not approved < 18 years
reboxetine (NE reuptake inhibitor)	Not recommended < 18 years	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) *Not on the official site (ANSM)*	*Not on the official site*
tianeptine (glutamate, opioid, unclear)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* No data available < 18 years, contraindication < 15 years (ANSM)	*Not on the official site*
trazodone (SER multimodal)	Contraindicated < 18 years	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) *Not on the official site (ANSM)*	Not approved < 18 years

Table S1. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
vilazodone (SER multimodal)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not approved < 18 years
vortioxetine (SER multimodal)	Not recommended < 18 years	Not recommended < 18 years (EMA) Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	Not studied < 18 years

NbN: Neuroscience-based Nomenclature, Second Edition Revised, Official NbN App (nbn2r.com); DA: dopamine; GABA: gamma aminobutyric acid; NC: not classified; NE: norepinephrine; PAM: positive allosteric modulator; SER: serotonin; EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration; d: day; min: minimum; max: maximum; SmPC: summary of product characteristics. If the formulation is not specified in the table, the indications correspond to an oral form only. [a]If the drug was on the FDA website, but without any SmPC available, information from the DailyMed database is provided. The authors have made every effort to ensure the accuracy of the information; however, an error, inaccuracy or misinterpretation of the official data cannot be totally excluded, particularly for some drugs where the approved diagnoses, ages or doses were not clearly formulated in the SmPC. The authors decline any responsibility for use of the information provided here. Furthermore, this information can evolve over time, so prescribers must always refer to current information on official websites. Last update December 2020.

Table S2. Antipsychotics' approval status in children and adolescents for psychiatric indications

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
Typical antipsychotics			
chlorpromazine (DA, SER antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* **Schizophrenia / Autism ≥ 1 year** (MHRA) Oral: < 1 year: for life saving only 1-5 years: 0.5 mg/kg every 4-6 h, max 40 mg/d 6-12 years: 1/3-1/2 adult dose, max 75 mg/d > 12 years: indications and pediatric doses not specified Short-acting injection: < 1 year: for life saving only 1-5 years: 0.5 mg/kg every 6-8 h, max 40 mg/d 6-12 years: 0.5 mg/kg every 6-8 h, max 75 mg/d > 12 years: indications and pediatric doses not specified No information in the SmPC about < 18 years for the other indications (psychoses, mania, hypomania, anxiety, agitation, dangerous behavior) **Severe behavioral problems with aggressiveness and agitation ≥ 3** (drops) **or 6** (tablet) **years** (ANSM) Oral: 1-5 mg/kg/d Short-acting injection: only for adults	**Severe behavioral problems / Hyperactivity with excessive motor activity and conduct disorders (short term) ≥ 6 months** (DailyMed) Tablet: start with low doses and increase dosage gradually 6 months-12 years: outpatients 0.25 mg/lb every 4-6 h if needed, hospitalized 50-100 mg/d (older children 200 mg/d or more), max 500 mg/d > 12 years: indications and pediatric doses not specified Short-acting injection: start with low doses and increase dosage gradually 6 months-12 years: outpatients 0.25 mg/lb every 6-8 h if needed, hospitalized max 40 mg/d (< 5 years or 50 lb) or max 75 mg/d except in unmanageable cases (5-12 years or 50-100 lb) > 12 years: indications and pediatric doses not specified. No information in the SmPC about < 18 years for the other indications (psychotic disorders, schizophrenia, mania)
chlorprothixene (DA, SER antagonist)	Not recommended < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*
clotiapine (NC)	Not studied < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
cyamemazine (DA, SER antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* **Severe behavioral problems with aggressiveness and agitation ≥ 3** (drops) **or 6** (tablet) **years** (ANSM) 1-4 mg/kg/d	*Not on the official site*
droperidol (NC)	No psychiatric indication	*Not centrally authorized (EMA)* No psychiatric indication (MHRA) Only for adults (but suggested for use in adolescents for agitation and aggressiveness states in psychosis at reduced dose under Posology section) (ANSM)	No psychiatric indication (DailyMed)
flupentixol (DA, SER antagonist)	Not studied < 18 years	*Not centrally authorized (EMA)* Tablet: not recommended < 18 years (MHRA) Long-acting injection: not indicated < 18 years (MHRA) No information in the SmPC about < 18 years (ANSM)	*Not on the official site*
fluphenazine (DA antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) Only for adults (ANSM)	Oral and short-acting injection: not established < 18 years (DailyMed) Long-acting injection: not established < 18 years, contraindicated < 12 years

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
haloperidol (DA antagonist)	**Schizophrenia ≥ 13 years** in second intention Oral: 0.5-3 mg/d (divided in two or three intakes), max 5 mg/d **Severe and persistent aggressiveness in autism or pervasive developmental disorders ≥ 6 years** in second intention Oral: 6-11 years: 0.5-3 mg/d (divided in two or three intakes), reevaluate after 6 weeks 12-17 years: 0.5-5 mg/d (divided in two or three intakes), reevaluate after 6 weeks **Severe tics (including Tourette syndrome) ≥ 10 years** in second intention Oral: 0.5-3 mg/d (divided in two or three intakes), reevaluate every 6-12 months Short- and long-acting injections: not established < 18 years	*Not centrally authorized (EMA)* **Schizophrenia ≥ 13 years** in second intention (MHRA and ANSM) Oral: 0.5-3 mg/d (divided in two or three intakes), max 5 mg/d **Severe and persistent aggressiveness in autism or pervasive developmental disorders ≥ 6 years** in second intention (MHRA and ANSM) Oral: 6-11 years: 0.5-3 mg/d (divided in two or three intakes), reevaluate after 6 weeks 12-17 years: 0.5-5 mg/d (divided in two or three intakes), reevaluate after 6 weeks **Severe tics (including Tourette syndrome) ≥ 10 years** in second intention (MHRA and ANSM) Oral: 0.5-3 mg/d (divided in two or three intakes), reevaluate after 6-12 months Indications, ages and dosages depending on the SmPC for MHRA (not included above)[b] Short- and long-acting injections: not recommended < 18 years	**Psychotic disorders ≥ 3 years** (DailyMed) Oral: 3-12 years (15-40 kg): start 0.5 mg/d, increase by 0.5 mg/d after 5-7 days if needed, maintenance 0.05-0.15mg/kg/d > 12 years: indications and pediatric doses not specified **Severe behavioral problems / Hyperactivity with excessive motor activity and conduct disorders (short term) / Tics in Tourette disorder ≥ 3 years** after failure to respond to psychotherapy or medications other than antipsychotics (DailyMed) Oral: 3-12 years (15-40 kg): start 0.5 mg/d, increase by 0.5 mg/d after 5-7 days if needed, maintenance 0.05-0.075 mg/kg/d > 12 years: indications and pediatric doses not specified Short- (DailyMed) and long-acting injections: not established < 18 years
levomepromazine (DA, SER antagonist)	Not studied < 18 years	*Not centrally authorized (EMA)* **Alternative to chlorpromazine in schizophrenia to decrease psychomotor activity < 18 years** (MHRA) Tablet: 12.5-25 mg/d, max 37.5 mg/d Should not be used < 18 years depending on the SmPC Injection: no psychiatric indication **Severe behavioral problems ≥ 3 years** (ANSM) Oral solution: 0.5-2 mg/kg/d, < 6 years only exceptional use in specialised environment Contraindicated < 1 year Injection and tablet: only for adults	*Not on the official site*

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
loxapine (DA, SER antagonist)	*Not on the official site*	Inhalation powder: not established < 18 years (EMA) *Not on the official site (MHRA)* **Psychotic disorders ≥ 15 years** (ANSM) Oral: 75-200 mg/d, max 600 mg/d **Agitation, aggressiveness or anxiety associated with psychotic disorders ≥ 15 years** (ANSM) Injection: 50-300 mg/d (divided in two or three injections) Contraindicated < 15 years (oral and injection) Inhalation powder: centrally evaluated, SmPC available on the EMA site	Not established < 18 years
molindone (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not recommended < 12 years for schizophrenia (DailyMed) Pediatric doses not specified
perphenazine (DA antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Indicated only in adults (but not recommended < 12 years for schizophrenia in the Warnings section)
pimozide (DA antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* **Schizophrenia ≥ 12 years** (MHRA) Start 2 mg/d, max 20 mg/d **Psychoses ≥ 12 years** (MHRA) Start 4 mg/d, max 16 mg/d **Tics in Tourette disorder / Severe behavioral problems particularly in autistic syndromes ≥ 6 years** (ANSM) 0.02-0.2 mg/kg/d	**Severe tics in Tourette disorder ≥ 12 years** in second intention (DailyMed) Start 0.05 mg/kg/d, increase every 3 days if needed, max 0.2 mg/kg/d, max 10 mg/d

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
pipamperone (NC)	Not recommended < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* **Agitation and aggressiveness in psychotic states ≥ 5 years** (ANSM) Only exceptional use in children Drops: start 10 mg/d, increase by 10 mg/d, target 10 mg x years of age Tablet: only for adults	*Not on the official site*
prochlorperazine (NC)	*Not on the official site*	*Not centrally authorized (EMA)* No psychiatric indication < 18 years (MHRA) *Not on the official site (ANSM)*	**Schizophrenia ≥ 2 years (or ≥ 20 lb)** Tablet (DailyMed): 2-12 years: start 5-7.5 mg/d (divided in two or three intakes), max 10 mg/d the first day, max 20 mg/d (2-5 years) or max 25 mg/d (6-12 years) after the first day > 12 years: pediatric doses not specified Short-acting injection: 2-12 years: 0.06 mg/lb/dose, switch to oral form as soon as possible > 12 years: pediatric doses not specified Suppository: No psychiatric indication Contraindicated < 2 years or < 20 lb
promazine (NC)	**Acute crisis of chronic psychotic disorders ≥ 12 years** 25 mg every 4-6 h	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) *Not on the official site (ANSM)*	*Not on the official site*

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
sulpiride (DA antagonist)	Not studied < 18 years	*Not centrally authorized (EMA)* Not recommended < 14 years for schizophrenia (MHRA) Pediatric doses not specified **Severe behavioral problems particularly in autistic syndromes ≥ 6 years** (ANSM) Oral: 5-10 mg/kg/d Oral solution < 6 years: only exceptional use in specialised environment Tablet 200 mg: only for adults	*Not on the official site*
thioridazine (DA, SER antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**Schizophrenia < 18 years** (DailyMed) Start 0.5 mg/kg/d in divided doses, max 3 mg/kg/d
thiothixene (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not recommended < 12 years for schizophrenia (DailyMed) Pediatric doses not specified
tiapride (DA antagonist)	**Severe tics ≥ 7 years** after failure to respond to a non-pharmacological treatment 7-12 years: 100-150 mg/d (divided in two or three intakes) > 12 years: 300 mg/d (divided in three intakes)	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* **Severe tics in Tourette disorder ≥ 6 years** (tablet) **or ≥ 17 kg** (oral solution) when a non-pharmacological treatment is not sufficient (ANSM) Oral: 3-6 mg/kg/d, max 300 mg/d Oral solution < 6 years: only exceptional use in specialised environment Injection (for other indications): only for adults	*Not on the official site*

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
trifluoperazine (DA, SER antagonist)	*Not on the official site*	*Not centrally authorized (EMA)*	**Schizophrenia ≥ 6 years** (DailyMed) 6-12 years: 1 mg/d, max 15 mg/d, > 15 mg/d possible for older children > 12 years: pediatric doses not specified
		Adjunct treatment for anxiety or agitation ≥ 3 years (MHRA) 3-5 years (oral solution and syrup only): max 1 mg/d in divided doses 6-12 years: max 4 mg/d in divided doses > 12 years: recommended 2-4 mg/d in divided doses, max 6 mg/d **Schizophrenia / Psychoses / Adjunct treatment for severe agitation or impulsive behavior ≥ 6 years** (MHRA) 6-12 years: start 5 mg/d in divided doses, increase with caution after min 3 days if needed (take into consideration the lower weights and the age) > 12 years: start 10 mg/d (divided in two intakes), increase by 5 mg/d after 1 week if needed, then increase by 5 mg/d after min 3 days if needed Indications depending on the SmPC	
		Not on the official site (ANSM)	
zuclopenthixol (DA antagonist)	Not studied < 18 years	*Not centrally authorized (EMA)* Tablet: Not indicated < 18 years (MHRA) Long-acting injection: Not recommended < 18 years (MHRA)	*Not on the official site*
		Long-acting injection: **Severe behavioral problems in children with agitation and aggressiveness** (ANSM)[c] Pediatric doses not specified Oral and intermediate-acting injection: no information in the SmPC about < 18 years	

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
Atypical antipsychotics			
amisulpride (DA antagonist)	Not recommended < 18 years, contraindicated < 15 years	*Not centrally authorized (EMA)* Should not be used < 18 years, contraindicated < 15 years (MHRA and ANSM)	No psychiatric indication
aripiprazole (DA, SER partial agonist, antagonist)	**Schizophrenia / Acute manic or mixed episodes in bipolar I disorder ≥ 13 years** Oral: start 2 mg/d for 2 days, then 5 mg/d for 2 days, then target 10 mg/d, increase by 5 mg/d if needed, max 30 mg/d, max 4 weeks for manic or mixed episodes Short-acting injection: not studied < 18 years Long-acting injection: not indicated < 18 years	**Schizophrenia ≥ 15 years** (EMA, MHRA, ANSM) Oral: start 2 mg/d for 2 days, then 5 mg/d for 2 days, then target 10 mg/day, increase by 5 mg/d if needed, max 30 mg/d **Manic episodes in bipolar I disorder ≥ 13 years** (EMA, MHRA, ANSM) Oral: start 2 mg/d for 2 days, then 5 mg/d for 2 days, then 10 mg/day, enhanced efficacy > 10 mg/d has not been demonstrated, max 12 weeks Short-acting injection: not studied < 18 years Long-acting injection: not established < 18 years Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	**Schizophrenia ≥ 13 years** Oral: start 2 mg/d for 2 days, then 5 mg/d for 2 days, then target 10 mg/d, increase by 5 mg/d if needed, max 30 mg/d **Acute manic or mixed episodes in bipolar I disorder ≥ 10 years** Oral: start 2 mg/d for 2 days, then 5 mg/d for 2 days, then target 10 mg/d, increase by 5 mg/d if needed, max 30 mg/d **Irritability in autistic disorders ≥ 6 years** Oral: start 2 mg/d, increase to 5 mg/d, then to 10-15 mg/d if needed with adjustments of up to 5 mg/d at intervals of no less than 1 week, max 15 mg/d **Tourette disorder ≥ 6 years** Oral: < 50 kg: start 2 mg/d for 2 days, then target 5 mg/d, increase to 10 mg/d after min 1 week if needed, max 10 mg/d ≥ 50 kg: start 2 mg/d for 2 days, then 5 mg/d for 5 days, then target 10 mg/d, increase by 5 mg/d after min 1 week if needed, max 20 mg/d Tablet with sensor: not established < 18 years Short-acting injection: indicated only in adults Long-acting injection: not studied < 18 years
asenapine (DA, SER, NE antagonist)	Not established < 18 years	Not indicated < 18 years (EMA) Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	**Acute manic or mixed episodes in bipolar I disorder ≥ 10 years** Start 5 mg/d (divided in two intakes), double the dosage with 3 days interval if needed, max 20 mg Transdermal: not established < 18 years

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
brexpiprazole (DA, SER partial agonist, antagonist)	Not studied < 18 years	Not established < 18 years (EMA) *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
cariprazine (DA, SER partial agonist, antagonist)	Not established < 18 years	Not established < 18 years (EMA) *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
clozapine (DA, SER, NE antagonist)	Not studied < 18 years	*Not centrally authorized (EMA)* Should not be used < 16 years for resistant schizophrenia or psychosis in Parkinson disease (MHRA) Pediatric doses not specified Must not be used < 16 years for resistant schizophrenia or psychosis in Parkinson disease (ANSM) Pediatric doses not specified	Not established < 18 years
lloperidone (SER, DA antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
lurasidone (DA, SER antagonist)	Not established < 18 years	**Schizophrenia ≥ 13 years** (EMA) Start 37 mg/d, max 74 mg/d Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	**Schizophrenia ≥ 13 years** Start 40 mg/d, max 80 mg/d **Depressive episodes in bipolar I disorder ≥ 10 years** Start 20 mg/d, increase after 1 week if needed, max 80 mg/d
olanzapine (DA, SER antagonist)	Contraindicated < 18 years	Not indicated < 18 years (EMA) Not indicated < 18 years (MHRA) Not indicated < 18 years (ANSM)	**Schizophrenia / Manic or mixed episodes in bipolar I disorder ≥ 13 years** in second intention Oral: start 2.5-5 mg/d, increase by 2.5-5 mg/d, target 10 mg/d, max 20 mg/d Short-acting injection: indicated only in adults Long-acting injection: not studied < 18 years

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
paliperidone (DA, SER, NE antagonist)	Must not be used < 18 years	**Schizophrenia ≥ 15 years** (EMA) Tablet: start 3 mg/d, increase by 3 mg/d after min 5 days if needed, max 6 mg/d (< 51 kg) or max 12 mg/d (≥ 51 kg) Long-acting injection: not established < 18 years Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	**Schizophrenia ≥ 12 years** Tablet: start 3 mg/d, increase by 3 mg/d after 5 days if needed, max 6 mg/d (< 51 kg) or max 12 mg/d (≥ 51 kg) Not established < 18 years depending on the SmPC Long-acting injection: not recommended < 18 years
pimavanserin (SER antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
quetiapine (DA, SER, NE multimodal)	**Schizophrenia ≥ 13 years** IR: start 50 mg/d the 1st day, 100 mg/d the 2nd, 200 mg/d the 3rd, 300 mg/d the 4th, and 400 mg/d the 5th, always divided in two or three intakes, then increase by 100 mg/d if needed, max 800 mg/d **Acute manic episodes in bipolar disorders ≥ 10 years** IR: start 50 mg/d the 1st day, 100 mg/d the 2nd, 200 mg/d the 3rd, 300 mg/d the 4th, and 400 mg/d the 5th, always divided in two or three intakes, then increase by 100 mg/d if needed, max 600 mg/d, max 3 weeks ER: must not be used < 18 years	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) Not recommended < 18 years (ANSM)	**Schizophrenia ≥ 13 years** IR: start 50 mg/d the 1st day, 100 mg/d the 2nd, 200 mg/d the 3rd, 300 mg/d the 4th, and 400 mg/d the 5th, always divided in two or three intakes, then increase by 100 mg/d if needed, max 800 mg/d ER: start 50 mg/d the 1st day, 100 mg/d the 2nd, 200 mg/d the 3rd, 300 mg/d the 4th, and 400 mg/d the 5th, max 800 mg/d **Acute manic episodes in bipolar I disorder ≥ 10 years** IR: start 50 mg/d the 1st day, 100 mg/d the 2nd, 200 mg/d the 3rd, 300 mg/d the 4th, and 400 mg/d the 5th, always divided in two or three intakes, then increase by 100 mg/d if needed, max 600 mg/d, max 3 weeks ER: start 50 mg/d the 1st day, 100 mg/d the 2nd, 200 mg/d the 3rd, 300 mg/d the 4th, and 400 mg/d the 5th, max 600 mg/d, max 3 weeks ER: not approved < 18 years depending on the SmPC

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
risperidone (DA, SER, NE antagonist)	**Behavioral and sociability disorders in mental retardation ≥ 5 years** < 50 kg: start 0.25 mg/d, increase by 0.25 mg/d after min 2 days if needed, recommended 0.5 mg/d, max 0.75 mg/d ≥ 50 kg: start 0.5 mg/d, increase by 0.5 mg/d after min 2 days if needed, recommended 1 mg/d, max 1.5 mg/d **Hyperactivity and irritability in autistic disorders ≥ 5 years** < 50 kg: start 0.25 mg/d, increase by 0.25 mg/d after min 4 days, recommended 0.5 mg/d, increase by 0.25 mg/d every 2 weeks if needed, max 1.25 mg/d (< 20 kg) or max 2.5 mg/d (≥ 20 kg) ≥ 50 kg: start 0.5 mg/d, increase by 0.5 mg/d after min 4 days, recommended 1 mg/d, increase by 0.5 mg/d every 2 weeks if needed, max 3.5 mg/d **Manic episodes in bipolar disorders ≥ 15 years** Start 2 mg/d, increase by 1 mg/d if needed, max 6 mg/d, max 12 weeks Long-acting injection: must not be used < 18 years	*Not centrally authorized (EMA)* **Persistent aggressiveness in conduct disorders with mental retardation ≥ 5 years** (MHRA and ANSM) < 50 kg: start 0.25 mg/d, increase by 0.25 mg/d after min 2 days if needed, max 0.75 mg/d, max 6 weeks ≥ 50 kg: start 0.5 mg/d, increase by 0.5 mg/d after min 2 days if needed, max 1.5 mg/d, max 6 weeks Long-acting injection: not established < 18 years	**Schizophrenia ≥ 13 years** Start 0.5 mg/d, increase by 0.5-1 mg/d after min 1 day if needed, recommended 3 mg/d, max 6 mg/d **Acute manic or mixed episodes in bipolar I disorder ≥ 10 years** Start 0.5 mg/d, increase by 0.5-1 mg/d after min 1 day if needed, recommended 1-2.5 mg/d, max 6 mg/d **Irritability in autistic disorders ≥ 5 years** < 20 kg: start 0.25 mg/d, increase by 0.25 mg/d after min 4 days, recommended 0.5 mg/d, increase by 0.25 mg/d every 2 weeks if needed, max 3 mg/d ≥ 20 kg: start 0.5 mg/d, increase by 0.5 mg/d after min 4 days, recommended 1 mg/d, increase by 0.5 mg/d every 2 weeks if needed, max 3 mg/d Long-acting injection: not established < 18 years
sertindole (DA, SER antagonist)	Not studied < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*

Table S2. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
ziprasidone (DA, SER antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years

NbN: Neuroscience-based Nomenclature, Second Edition Revised, Official NbN App (nbn2r.com); DA: dopamine; NC: not classified; NE: norepinephrine; SER: serotonin; EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration; d: day; h: hour; lb: pounds (1 kg = 2.2 lb); min: minimum; max: maximum; IR: immediate release; ER: extended release; SmPC: summary of product characteristics. If the formulation is not specified in the table, the indications correspond to an oral form only. [a]If the drug was on the FDA website, but without any SmPC available, information from the DailyMed database is provided. [b]For MHRA, the following indications for oral haloperidol could also be noted in other SmPC (without minimal age specified): childhood schizophrenia, childhood behavioral problems especially when associated with hyperactivity and aggression, and Gilles de La Tourette syndrome, with max dosages of 10 mg/d. [c]We found inconsistent that the depot form of zuclopenthixol is indicated in children, but not the oral form. The authors have made every effort to ensure the accuracy of the information; however, an error, inaccuracy or misinterpretation of the official data cannot be totally excluded, particularly for some drugs where the approved diagnoses, ages or doses were not clearly formulated in the SmPC. The authors decline any responsibility for use of the information provided here. Furthermore, this information can evolve over time, so prescribers must always refer to current information on official websites. Last update December 2020.

Table S3. Anxiolytics' and hypnotics'/sedatives' approval status in children and adolescents for psychiatric indications

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
Anxiolytics			
Benzodiazepines			
alprazolam (GABA PAM)	Not recommended < 18 years	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) Must not be used < 18 years (ANSM)	Not studied < 18 years
bromazepam (GABA PAM)	**Anxiety < 18 years** Only if benefit/risk ratio is favorable, dose must be adapted to children's low body weight, max 8-12 weeks	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* Not recommended < 18 years (ANSM), but suggested for use for anxiety and alcohol withdrawal after evaluation of the benefit/risk ratio, for the shortest duration of treatment and at a reduced dose compared to adults (1/2 for example)	*Not on the official site*
chlordiazepoxide (GABA PAM)	*Not on the official site*	*Not centrally authorized (EMA)* Not indicated < 18 years (MHRA) *Not on the official site (ANSM)*	**Anxiety disorders ≥ 6 years** (DailyMed) 10-20 mg/d (divided in two to four intakes), max 20-30 mg/d (divided in two or three intakes)
chlordiazepoxide + clidinium (GABA PAM + NC)	Not recommended < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
clobazam (NC)	**Anxiety ≥ 3 years** 3-15 years: 5-10 mg/d (if 10 mg/d divided in two intakes) > 15 years: 15 mg/d (divided in three intakes) Max 4-12 weeks	*Not centrally authorized (EMA)* No psychiatric indication < 18 years (MHRA) No psychiatric indication < 18 years (ANSM)	No psychiatric indication
clonazepam (GABA PAM)	No psychiatric indication	*Not centrally authorized (EMA)* No psychiatric indication (MHRA) No psychiatric indication (ANSM)	No psychiatric indication < 18 years

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
clorazepate (GABA PAM)	**Anxiety ≥ 9 years** 0.5 mg/kg/d in divided doses, only exceptional use, max 2-4 weeks Contraindicated < 9 years Injection: no psychiatric indication < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* **Anxiety / Alcohol withdrawal ≥ 6 years** (ANSM) 0.5 mg/kg/d (in divided doses), only exceptional use, max 8-12 weeks for anxiety, max 8-10 days for alcohol withdrawal Capsule > 5 mg and injection: only for adults	No psychiatric indication < 18 years
clotiazepam (GABA PAM)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* Not recommended < 18 years (ANSM)	*Not on the official site*
diazepam (GABA PAM)	**Anxiety / Agitation / Delirium tremens ≥ 6 months** Tablet/injection: 0.1-0.3 mg/kg/d, only after a careful evaluation of the indication, for the shortest duration of treatment Drops: not recommended < 18 years Rectal: no psychiatric indication	*Not centrally authorized (EMA)* **Night terrors / Somnambulism < 18 years** (MHRA) Oral: 1-5 mg/d at bedtime Indications depending on the SmPC **Anxiety / Agitation ≥ 1 year** (MHRA) Rectal: ≥ 1 year: 0.5 mg/kg, or: 1-3 years (10-15 kg): 5 mg ≥ 3 years (≥ 15 kg): 10 mg Repeat every 12 h if needed Dosage depending on the SmPC Injection: no psychiatric indication < 18 years **Anxiety / Alcohol withdrawal ≥ 6 years** (ANSM) Tablet: reduced dose compared to adults (1/2 for example), only exceptional use Injection and oral solution: no psychiatric indication < 18 years	**Anxiety / Alcohol withdrawal ≥ 6 months** Start 3-10 mg/d (divided in three or four intakes), increase gradually if needed Contraindicated < 6 months Nasal spray and rectal gel: no psychiatric indication Injection: no psychiatric indication < 18 years (Dailymed)
ethyl loflazepate (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* Only for adults (ANSM)	*Not on the official site*

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
ketazolam (NC)	Not studied < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*
lorazepam (GABA PAM)	Oral: contraindicated < 12 years for anxiety / excitation Pediatric doses not specified Injection: contraindicated < 18 years	*Not centrally authorized (EMA)* Oral: should not be used < 18 years or not recommended < 13 years for anxiety depending on the SmPC (MHRA) Pediatric doses not specified Injection: not recommended < 12 years for anxiety (MHRA) Pediatric doses not specified Not recommended < 18 years (but suggested for use in children for anxiety / alcohol withdrawal at a half dose under Posology section depending on the SmPC) (ANSM)	Oral: not established < 12 years for anxiety Pediatric doses not specified Injection: no psychiatric indication < 18 years
nordazepam (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* Only for adults (ANSM)	*Not on the official site*
oxazepam (GABA PAM)	Contraindicated < 12 years for anxiety / excitation / alcohol withdrawal Pediatric doses not specified	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) Not recommended < 18 years (ANSM)	Not indicated < 6 years and absolute dosage not established 6-12 years for anxiety / alcohol withdrawal (DailyMed) Pediatric doses not specified
prazepam (GABA PAM)	**Anxiety / Agitation ≥ 3 years** 3-12 years: 10-15 mg/d (divided in two or three intakes) > 12 years: pediatric doses not specified	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* **Anxiety ≥ 12 years** (ANSM) Max 1 mg/kg/d Contraindicated < 6 years Only for adults or not recommended < 18 years but suggested for use in pediatrics at a half dose depending on the SmPC	*Not on the official site*

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
Other anxiolytics			
buspirone (SER partial agonist)	*Not on the official site*	*Not centrally authorized (EMA)* Should not be used < 18 years (MHRA) Not recommended < 18 years (ANSM)	Not superior to placebo for general anxiety disorder < 18 years (DailyMed)
etifoxine (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* No information in the SmPC about < 18 years (ANSM)	*Not on the official site*
hydroxyzine (histamine antagonist)	No psychiatric indication < 18 years	*Not centrally authorized (EMA)* No psychiatric indication < 18 years (MHRA) **Insomnia due to anxiety ≥ 3** (syrup) **or 6** (tablet) **years** only in second intention (ANSM) 1 mg/kg/d, max 2 weeks, max 2 mg/kg/d (< 40 kg) or max 100 mg/d (> 40 kg) Injection: exclusively reserved for adults	**Anxiety < 18 years** Oral: < 6 years: 50 mg/d in divided doses ≥ 6 years: 50-100 mg/d in divided doses Injection: no psychiatric indication < 18 years
magnesium orotate (NC)	Not studied < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*
meprobamate (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**Anxiety disorders ≥ 6 years** (DailyMed) 6-12 years: 200-600 mg/d (divided in two or three intakes) > 12 years: pediatric doses not specified
pregabalin (glutamate channel blocker)	Not recommended < 18 years	Should not be used < 18 years (EMA) Not recommended < 18 years (MHRA) Not recommended < 18 years (ANSM)	No psychiatric indication

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
Hypnotics/sedatives			
Benzodiazepines			
estazolam (GABA PAM)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* Not recommended < 18 years (but suggested for use in children for insomnia at a half dose under Posology section) (ANSM)	Not studied < 18 years (DailyMed)
flunitrazepam (GABA PAM)	Contraindicated < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*
flurazepam (GABA PAM)	Not indicated < 18 years	*Not centrally authorized (EMA)* Contraindicated < 18 years (MHRA) *Not on the official site (ANSM)*	Not established < 18 years, not recommended < 15 years (DailyMed)
loprazolam (NC)	*Not on the official site*	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) Not recommended < 18 years (but suggested for use in children for insomnia at a half dose under Posology section) (ANSM)	*Not on the official site*
lormetazepam (GABA PAM)	Not recommended < 18 years	*Not centrally authorized (EMA)* Must not be used without careful assessment < 18 years (MHRA and ANSM)	*Not on the official site*
midazolam (GABA PAM)	Tablet: contraindicated for psychiatric indication < 18 years Buccal solution and injection: no psychiatric indication	Not centrally authorized for psychiatric indication (EMA) Tablet: contraindicated < 18 years (MHRA) Buccal / Oral solution and injection: no psychiatric indication (MHRA) No psychiatric indication (ANSM)	No psychiatric indication

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
nitrazepam (GABA PAM)	Contraindicated for psychiatric indication < 18 years	*Not centrally authorized (EMA)* Contraindicated or not recommended < 12 or 18 years for insomnia depending on the SmPC (MHRA) Pediatric doses not specified Only for adults, contraindicated < 15 years (ANSM)	*Not on the official site*
quazepam (GABA PAM)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
temazepam (GABA PAM)	Not evaluated < 18 years	*Not centrally authorized (EMA)* Tablet: contraindicated < 18 years (MHRA) Oral solution: contraindicated or no psychiatric indication < 18 years depending on the SmPC (MHRA) *Not on the official site (ANSM)*	Not established < 18 years
triazolam (GABA PAM)	Not recommended < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
Other hypnotics/sedatives			
chloral hydrate (GABA PAM)	**Sleep disorders < 18 years** 30-50 mg/kg/d at bedtime, max 1 g **Excitation < 18 years** 25 mg/kg/d (divided in three or four intakes), max 1 g/single dose	*Not centrally authorized (EMA)* **Insomnia ≥ 2 years** (MHRA) 2-11 years: 30-50 mg/kg/d at bedtime, max 1 g/d, max 2 weeks ≥ 12 years: 430-860 mg/d at bedtime, max 2 g/d *Not on the official site (ANSM)*	*Not on the official site*
clomethiazole (GABA PAM)	Contraindication < 18 years	*Not centrally authorized (EMA)* Not recommended < 18 years (MHRA) *Not on the official site (ANSM)*	*Not on the official site*

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
diphenhydramine (histamine antagonist)	**Sleep disorders ≥ 2 years** 2-4 years (12-17 kg): 8-12 mg/d at bedtime (drops) 5-7 years (18-25 kg): 14-18 mg/d at bedtime (drops) 8-11 years (26-35 kg): 24-36 mg/d at bedtime (drops) ≥ 12 years: 50 mg/d at bedtime (drops or tablet) If sleep disorders persist after 2 weeks, reassess the treatment Contraindicated < 16 years depending on the SmPC	*Not centrally authorized (EMA)* **Sleep disorders ≥ 16 years** (MHRA) 50 mg/d at bedtime, max 2 weeks Contraindicated < 16 years depending on the SmPC No psychiatric indication (ANSM)	Oral: no psychiatric indication (DailyMed) Injection: no psychiatric indication
diphenhydramine + lorazepam (histamine antagonist + GABA PAM)	Not studied < 18 years	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	*Not on the official site*
doxylamine (NC)	**Nervousness associated with difficulties falling asleep ≥ 12 years** 10-30 mg/d (divided in two or three intakes if > 10 mg/d), max 50 mg/d (divided in five intakes) Contraindicated < 12 years	*Not centrally authorized (EMA)* No psychiatric indication (MHRA) Only for adults, contraindicated < 15 years (ANSM)	**Sleep disorders ≥ 12 years** 25 mg/d at bedtime
eszopiclone (GABA PAM)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* Contraindicated < 18 years (ANSM)	Not established < 18 years

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
melatonin (melatonin agonist)	**Insomnia in autism spectrum disorders or Smith-Magenis syndrome ≥ 2 years** Start 2 mg/d 30-60 minutes before bedtime, increase to 5 mg/d if needed, max 10 mg/d Not recommended < 18 years depending on the SmPC	**Insomnia in autism spectrum disorders or Smith-Magenis syndrome ≥ 2 years** (EMA) Start 2 mg/d 30-60 minutes before bedtime, increase to 5 mg/d if needed, max 10 mg/d Not established < 18 years depending on the SmPC **Insomnia in ADHD ≥ 6 years** (MHRA) Start 1-2 mg/d 30-60 minutes before bedtime, increase by 1 mg/d after 1 week if needed, max 5 mg/d Reevaluate after 3 months Indications depending on the SmPC Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	*Not on the official site*
methohexital (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	No psychiatric indication < 18 years
pentobarbital (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**Insomnia < 18 years** only for short-term (DailyMed) Intramuscular: 2-6 mg/kg, max 100 mg
ramelteon (melatonin agonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
secobarbital (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	No psychiatric indication < 18 years (DailyMed)
suvorexant (orexin antagonist)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years

Table S3. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
tasimelteon (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
zaleplon (GABA PAM)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	Not established < 18 years
zolpidem (GABA PAM)	Must not be used < 18 years	*Not centrally authorized (EMA)* Contraindicated or should not be used < 18 years depending on the SmPC (MHRA) Not recommended < 18 years (ANSM)	Not recommended < 18 years
zopiclone (GABA PAM)	Must not be used < 18 years	*Not centrally authorized (EMA)* Contraindicated < 18 years (MHRA) Contraindicated or not recommended < 18 years depending on the SmPC (ANSM)	*Not on the official site*

NbN: Neuroscience-based Nomenclature, Second Edition Revised, Official NbN App (nbn2r.com); GABA: gamma aminobutyric acid; NC: not classified; PAM: positive allosteric modulator; SER: serotonin; EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration; d: day; h: hour; max: maximum; SmPC: summary of product characteristics; ADHD: attention-deficit/hyperactivity disorder. If the formulation is not specified in the table, the indications correspond to an oral form only. [a]If the drug was on the FDA website, but without any SmPC available, information from the DailyMed database is provided. The authors have made every effort to ensure the accuracy of the information; however, an error, inaccuracy or misinterpretation of the official data cannot be totally excluded, particularly for some drugs where the approved diagnoses, ages or doses were not clearly formulated in the SmPC. The authors decline any responsibility for use of the information provided here. Furthermore, this information can evolve over time, so prescribers must always refer to current information on official websites. Last update December 2020.

Table S4. Mood stabilizers' approval status in children and adolescents for psychiatric indications

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA[a]**
carbamazepine (glutamate channel blocker)	No psychiatric indication < 18 years	*Not centrally authorized (EMA)* No psychiatric indication < 18 years (MHRA) No psychiatric indication < 18 years (ANSM)	No psychiatric indication
lamotrigine (glutamate channel blocker)	No psychiatric indication < 18 years	*Not centrally authorized (EMA)* No psychiatric indication < 18 years (MHRA) No psychiatric indication < 18 years (ANSM)	No psychiatric indication < 18 years
lithium (enzyme modulator)	**Acute phase and prophylaxis of bipolar disorders ≥ 12 years** Titrate to serum levels of 0.8-1.2 mmol/l for acute phase and to 0.5-0.8 mmol/l for prophylaxis **Combination with antidepressants for resistant depression ≥ 12 years** Titrate to serum levels of 0.5-0.8 mmol/l **Severe chronic aggressiveness ≥ 12 years** Titration not specified Indications depending on the SmPC For all indications, only in hospitals with required experience	Not centrally authorized for psychiatric indication (EMA) Should not be used < 18 years (MHRA) Not recommended < 18 years (ANSM)	**Manic or mixed episodes and maintenance in bipolar I disorder ≥ 7 years** Titrate to serum levels of 0.8-1.2 mEq/l for acute treatment and to 0.8-1.0 mEq/l for maintenance
valproate (glutamate unclear)	No psychiatric indication < 18 years	Not centrally authorized for psychiatric indication < 18 years (EMA) No psychiatric indication < 18 years (MHRA) Not indicated < 18 years (ANSM)	No psychiatric indication < 18 years (DailyMed)

NbN: Neuroscience-based Nomenclature, Second Edition Revised, Official NbN App (nbn2r.com); EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration; SmPC: summary of product characteristics. For lithium: 1 mmol/l = 1 mEq/l. If the formulation is not specified in the table, the indications correspond to an oral form only. [a]If the drug was on the FDA website, but without any SmPC available, information from the DailyMed database is provided. The authors have made every effort to ensure the accuracy of the information; however, an error, inaccuracy or misinterpretation of the official data cannot be totally excluded, particularly for some drugs where the approved diagnoses, ages or doses were not clearly formulated in the SmPC. The authors decline any responsibility for use of the information provided here. Furthermore, this information can evolve over time, so prescribers must always refer to current information on official websites. Last update December 2020.

Table S5. Medications' approval status for ADHD in children and adolescents for psychiatric indications

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
Non-amphetamine psychostimulants			
dexmethylphenidate (DA, NE multimodal)	**ADHD ≥ 6 years** ER: start 5 mg/d, increase by 5 mg/d per week if needed, max 20 mg/d	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**ADHD ≥ 6 years** IR: start 5 mg/d (divided in two intakes), increase by 2.5-5 mg/d per week if needed, max 20 mg/d ER: start 5 mg/d, increase by 5 mg/d per week if needed, max 30 mg/d
methylphenidate (DA, NE multimodal)	**ADHD ≥ 6 years** IR: start 5-10 mg/d (in divided doses if ≥ 10 mg/d), increase by 5-10 mg/d per week if needed, max 60 mg/d ER: start 5-18 mg/d, increase by 5-18 mg/d per week if needed, max 54-60 mg/d in children or max 60-72 mg/d in adolescents, dosage depending on the SmPC	*Not centrally authorized (EMA)* **ADHD ≥ 6 years** (MHRA and ANSM) IR: start 5-10 mg/d (in divided doses if ≥ 10 mg/d), increase by 5-10 mg/d per week if needed, max 60 mg/d ER: start 5-18 mg/d, increase by 5-18 mg/d per week if needed, max 54-60 mg/d, dosage depending on the SmPC	**ADHD ≥ 6 years** IR: start 10 mg/d (divided in two intakes), increase by 5-10 mg/d per week if needed, max 60 mg/d ER: start 10-25 mg/d, increase by 5-20 mg/d per 5-7 days if needed, > 54-100 mg/d (6-12 years) and > 60-100 mg/d (13-17 years) not recommended, dosage depending on the SmPC Transdermal: start 10 mg/9h at week 1, increase if needed to 15 mg/9h at week 2, 20 mg/9h at week 3 and 30 mg/9h at week 4
Amphetamines psychostimulants			
amphetamine (DA, NE multimodal)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**ADHD ≥ 6 years** IR: start 5 mg/d, additional dose after 4-6h if needed, increase by 5 mg/d after 1 week if needed, max 40 mg/d ER: start 2.5-6.3 mg/d, increase by 2.5-10 mg/d after 4-7 days if needed, max 12.5-20 mg/d, dosage depending on the SmPC
amphetamine mixed salts + dextroamphetamine mixed salts (DA, NE multimodal)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**ADHD ≥ 6 years** (or ≥ 13 years) 6-12 years: start 5-10 mg/d, increase by 5-10 mg/d after 1 week if needed, max 30 mg/d 13-17 years: start 10-12.5 mg/d, increase to 20-25 mg/d after 1 week if needed Age and dosage depending on the SmPC

Table S5. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
dexamfetamine (DA, NE multimodal)	*Not on the official site*	*Not centrally authorized (EMA)* **ADHD ≥ 6 years** in second intention (MHRA) Start 5-10 mg/d (divided in two intakes if 10 mg/d), increase by 5 mg/d per week if needed, max 20-40 mg/d **Refractory hyperkinetic states ≥ 3 years** (MHRA) 3-5 years: start 2.5 mg/d, increase by 2.5 mg/d per week if needed, max 20 mg/d ≥ 6 years: start 5-10 mg/d, increase by 5 mg/d per week if needed, max 20-40 mg/d Indications depending on the SmPC *Not on the official site (ANSM)*	*Not on the official site*
lisdexamfetamine (DA, NE multimodal)	**ADHD ≥ 6 years** in second intention Start 20-30 mg/d, increase by 10-20 mg/d per week if needed, max 70 mg/d	*Not centrally authorized (EMA)* **ADHD ≥ 6 years** in second intention (MHRA) Start 20-30 mg/d, increase by 10-20 mg/d per week if needed, max 70 mg/d *Not on the official site (ANSM)*	**ADHD ≥ 6 years** Start 30 mg/d, increase by 10-20 mg/d per week if needed, recommended dose 30-70 mg/d, max 70 mg/d
methamphetamine (NC)	*Not on the official site*	*Not centrally authorized (EMA)* *Not on the official site (MHRA)* *Not on the official site (ANSM)*	**ADHD ≥ 6 years** Start 5-10 mg/d (divided in two intakes if 10 mg/d), increase by 5 mg/d after 1 week if needed, max 25 mg/d
Non-psychostimulants			
atomoxetine (NE reuptake inhibitor)	**ADHD ≥ 6 years** < 70 kg: start 0.5 mg/kg/d, increase to 0.8 mg/kg/d after 7-14 days if needed, increase to 1.2 mg/kg/d after 7-14 days if needed, max 1.2 mg/kg/d > 70 kg: start 40 mg/d, increase to 60 mg/d after 7-14 days if needed, increase to 80 mg/d after 7-14 days if needed, max 80 mg/d Contraindicated < 6 years	*Not centrally authorized (EMA)* **ADHD ≥ 6 years** (MHRA) < 70 kg: start 0.5 mg/kg/d, increase after min 7 days if needed, 1.2 mg/kg/d recommended > 70 kg: start 40 mg/d, increase after min 7 days if needed, 80-100 mg/d recommended *Not on the official site (ANSM)*	**ADHD ≥ 6 years** < 70 kg: start 0.5 mg/kg/d, increase to target 1.2 mg/kg/d after min 3 days, max 1.4 mg/kg/d > 70 kg: start 40 mg/d, increase to target 80 mg/d after min 3 days, increase to max 100 mg/d after 2-4 weeks if needed

Table S5. Continued

Drug (NbN)	**Swissmedic**	**EMA / MHRA / ANSM**	**FDA**[a]
clonidine (NE agonist)	No psychiatric indication	Not centrally authorized for psychiatric indication (EMA) No psychiatric indication (MHRA) No psychiatric indication (ANSM)	**ADHD ≥ 6 years** ER: Start 0.1 mg/d, increase by 0.1 mg/d per week if needed, max 0.4 mg/d, if > 0.1 mg/d divide in two intakes IR, injection and transdermal: no psychiatric indication
guanfacine (NE agonist)	**ADHD ≥ 6 years** in second intention Start 1 mg/d, increase by 1 mg/d per week if needed, recommended dose 0.05-0.12 mg/kg/d 6-12 years: max 4 mg/d (≥ 25 kg) 13-17 years: max 4 mg/d (≥ 34 kg), max 5 mg/d (≥ 41.5 kg), max 6 mg/d (≥ 49.5 kg) or max 7 mg/d (≥ 58.5 kg)	**ADHD ≥ 6 years** in second intention (EMA) Start 1 mg/d, increase by 1 mg/d per week if needed, recommended dose 0.05-0.12 mg/kg/d 6-12 years: max 4 mg/d (≥ 25 kg) 13-17 years: max 4 mg/d (≥ 34 kg), max 5 mg/d (≥ 41.5 kg), max 6 mg/d (≥ 49.5 kg) or max 7 mg/d (≥ 58.5 kg) Centrally evaluated, SmPC available on the EMA site (MHRA and ANSM)	**ADHD ≥ 6 years** Start 1 mg/d, increase by 1 mg/d per week if needed, recommended dose 1-7 mg/d (0.05-0.12 mg/kg/d), 2-3 mg/d (25-33.9 kg), 2-4 mg/d (34-41.4 kg), 3-5 mg/d (41.5-49.4 kg), 3-6 mg/d (49.5-58.4 kg), 4-7 mg/d (58.5-91 kg), 5-7 mg/d (> 91 kg), > 4 mg/d in children (6-12 years) and > 7 mg/d in adolescents (13-17 years) not evaluated

NbN: Neuroscience-based Nomenclature, Second Edition Revised, Official NbN App (nbn2r.com); DA: dopamine; NC: not classified; NE: norepinephrine; EMA: European Medicines Agency; MHRA: British Medicines and Healthcare Products Regulatory Agency; ANSM: French National Agency for the Safety of Medicines and Health Products; FDA: Food and Drug Administration; ADHD: attention-deficit/hyperactivity disorder; d: day; h: hour; min: minimum; max: maximum; IR: immediate release; ER: extended release; SmPC: summary of product characteristics. If the formulation is not specified in the table, the indications correspond to an oral form only. [a]If the drug was on the FDA website, but without any SmPC available, information from the DailyMed database is provided. The authors have made every effort to ensure the accuracy of the information; however, an error, inaccuracy or misinterpretation of the official data cannot be totally excluded, particularly for some drugs where the approved diagnoses, ages or doses were not clearly formulated in the SmPC. The authors decline any responsibility for use of the information provided here. Furthermore, this information can evolve over time, so prescribers must always refer to current information on official websites. Last update December 2020.