Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects

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Mental disorders frequently begin in childhood or adolescence. Psychotropic medications have various indications for the treatment of mental disorders in this age group and are used not infrequently off-label. However, the adverse effects of these medications require special attention during developmentally sensitive periods of life. For this meta-review, we systematically searched network meta-analyses and meta-analyses of randomized controlled trials (RCTs), individual RCTs, and cohort studies reporting on 78 a priori selected adverse events across 19 categories of 80 psychotropic medications – including antidepressants, antipsychotics, anti-attention-deficit/hyperactivity disorder (ADHD) medications and mood stabilizers – in children and adolescents with mental disorders. We included data from nine network meta-analyses, 39 meta-analyses, 90 individual RCTs, and eight cohort studies, including 337,686 children and adolescents. Data on ≥20% of the 78 adverse events were available for six antidepressants (sertraline, escitalopram, paroxetine, fluoxetine, venlafaxine and vilazodone), eight antipsychotics (risperidone, quetiapine, aripiprazole, lurasidone, paliperidone, ziprasidone, olanzapine and asenapine), three anti-ADHD medications (methylphenidate, atomoxetine and guanfacine), and two mood stabilizers (valproate and lithium). Among these medications with data on ≥20% of the 78 adverse events, a safer profile emerged for escitalopram and fluoxetine among antidepressants, lurasidone for antipsychotics, methylphenidate among anti-ADHD medications, and lithium among mood stabilizers. The available literature raised most concerns about the safety of venlafaxine, olanzapine, atomoxetine, guanfacine and valproate. Nausea/vomiting and discontinuation due to adverse event were most frequently associated with antidepressants; sedation, extrapyramidal side effects, and weight gain with antipsychotics; anorexia and insomnia with anti-ADHD medications; sedation and weight gain with mood stabilizers. The results of this comprehensive and updated quantitative systematic meta-review of top-tier evidence regarding the safety of antidepressants, antipsychotics, anti-ADHD medications and mood stabilizers in children and adolescents can inform clinical practice, research and treatment guidelines.

Key words: Safety, tolerability, children, adolescents, psychopharmacology, antidepressants, antipsychotics, mood stabilizers, psychostimulants, meta-review

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Childhood and adolescence are a crucial time of biopsychosocial development[1]. Many, if not most, severe mental disorders have their onset prior to age 18[2]. Early intervention is a cornerstone of modern psychiatry which has demonstrated superior outcomes, for example, in psychotic disorders and bipolar disorder[3,4]. In addition to psychotherapeutic and psychosocial interventions, psychotropic medications are often necessary to treat severe mental disorders that result in subjective distress and/or significant dysfunction in youth.

Several antidepressants, antipsychotics, anti-attention-deficit/hyperactivity disorder (ADHD) medications and mood stabilizers indicated in adults have received regulatory approval for use in children and/or adolescents[5], and many are used off-label[6-10]. However, despite evidence for the efficacy of a number of psychotropic medications in youth, the duration of untreated illness in depressive disorder[11], bipolar disorder[12,13], schizophrenia[14], obsessive-compulsive disorder[15], anxiety disorders[16], and other mental disorders[17] is often long[18,19], which adversely affects long-term outcomes[14,20-24]. Such delay can be related to several factors. These certainly include reduced access to care due to stigma and self-stigma surrounding mental illness[25-27], but stigma-derived or data-based concerns about the safety of psychotropic medications in children and adolescents are also relevant[28-34].

The poor quality of data on safety of psychotropic medications can potentially induce a delay or refusal of treatment, despite evidence that medications used in psychiatry are generally not less effective than those prescribed in other fields of medicine[35]. For instance, poor reporting of adverse events in available randomized controlled trials (RCTs) may have led to inaccurate estimates of some serious events, such as suicidality with antidepressants[36]. In addition, regulatory agencies may issue boxed warnings for adverse events of medications, such as for antidepressants increasing suicidality in children, adolescents and young adults[37], which can impact prescribing habits in everyday clinical practice[38], but whose validity may then be ques-

tioned[39,40]. At the same time, evidence-based safety concerns and warnings are essential to inform treatment guidelines and clinical care and are crucial to protect patients according to the *primum non nocere* principle.

The evidence on safety of psychotropic agents in children and adolescents with mental disorders has been rapidly growing[41], but remains fragmented. The available network meta-analyses (NMAs) and meta-analyses (MAs) have generally considered efficacy as their primary outcome, while safety is usually not prioritized in the primary RCTs and related evidence syntheses. Moreover, NMAs and MAs only include RCTs, usually concerning one or, rarely, few related mental disorders.

While RCTs minimize the influence of several sources of bias on estimates of medication effects in a specific population, they also apply strict selection criteria, which reduces the generalizability and external validity of their findings. Moreover, RCTs are often relatively small and short in duration, which precludes the adequate identification of rare but serious or long-term adverse events[42]. Furthermore, NMAs and MAs generally focus on the use of medications in disorders for which they are indicated, excluding evidence about off-label use. Therefore, a comprehensive summary of the evidence concerning the safety of psychotropic medications for all the mental health conditions for which they are used in children and adolescents, based on RCTs as well as on large cohort studies including more generalizable samples and reflecting real-world use patterns, is important to inform clinical practice.

To the best of our knowledge, no systematic meta-review exists to date that has focused on the safety of psychotropic drugs in children and adolescents as its primary outcome, summarizing data from NMAs, MAs, largest individual RCTs, and well-designed matched cohort studies across all relevant mental disorders. The aim of the present meta-review was to provide the largest and most comprehensive evidence synthesis on the safety of four major psychotropic medication classes (antidepressants, antipsychotics, anti-ADHD drugs, mood stabilizers) in children and adolescents with mental disorders, in order to inform clinical decision making and guideline development, and to identify areas needing further research.

METHODS

Search, inclusion and exclusion criteria

This systematic meta-review followed an *a priori* protocol (available upon request). We conducted a systematic search in PubMed and PsycINFO, from database inception up to September 7, 2019, using an exhaustive combination of key words for both psychotropic medications and adverse health outcomes (full search string available upon request). Additional manual searches were performed on reference lists of included articles. Pairs of authors conducted title/abstract screening and full-text assessment, and extracted data into a pre-defined excel spreadsheet. A third author resolved any conflict.

Inclusion criteria were: a) NMAs, MAs, individual RCTs, and cohort studies controlling for confounding by indication (i.e., medication vs. placebo/no medication in subjects affected by the same disorder); b) data on the association between antidepressants, antipsychotics, anti-ADHD medications, or mood stabilizers and adverse health outcomes; c) population of children and/or adolescents with any mental disorder.

Exclusion criteria were: a) studies on conditions other than mental disorders for which psychotropic medications are indicated or used (e.g., epilepsy); b) confounding by indication (i.e., comparing patients on medications with healthy controls), even if they adjusted analyses for covariates; c) designs other than those indicated in inclusion criteria; d) no data on the association between the targeted medications and adverse health outcomes.

Included adverse events and psychotropic medications

The 78 *a priori* selected adverse events were subdivided into the following 19 categories: central nervous system (agitation, anxiety, asthenia, irritability, cognitive impairment, depression, dizziness, headache, mania, psychosis, sedation, insomnia, seizures, suicidal ideas/behaviors/attempts); nutritional and metabolic (anorexia, binge eating/increased appetite, increased cholesterol, increased triglycerides, metabolic syndrome, glucose dysregulation/diabetes, insulin resistance, increased waist circumference, weight gain/increased body mass index, weight loss); cardiovascular (arrhythmias/tachycardia, cardiomyopathy, cerebrovascular disease, coronary heart disease, hypertension, hypotension, myocarditis, QT prolongation, sudden cardiac death); gastrointestinal (abdominal pain, constipation, diarrhea, gastrointestinal symptoms, liver damage, nausea/vomiting); genitourinary (enuresis, kidney disease/failure, menstrual cycle alterations, polycystic ovarian syndrome, sexual dysfunction); movement disorders (akathisia, any extrapyramidal side effect, tremor, dystonia, tardive dyskinesia); impulse dyscontrol and risky behavior (criminal behavior, gambling, substance abuse, non-suicidal self-injury behaviors); endocrine (gynecomastia/galactorrhea, hypo/hyperprolactinemia, hypo/hyperthyroidism); hematologic (anemia, leukocytopenia, thrombocytopenia); mouth (dental caries, dry mouth, sialorrhea); respiratory (acute respiratory failure, asthma, nasopharyngitis/upper respiratory tract infection/pneumonia); venous thromboembolism (deep vein thrombosis, pulmonary embolism); bone health (osteopenia/osteoporosis, fractures); accidents (any accident, fall); neuroleptic malignant syndrome (neuroleptic malignant syndrome/fever/creatine phosphokinase elevation); any cancer; discontinuation due to adverse event; serious adverse events; and mortality (all-cause, due to natural causes, due to suicide).

The 80 psychotropic medications were subdivided into the four categories of antidepressants, antipsychotics, anti-ADHD medications, and mood stabilizers. The category of antidepressants included nine classes: monoamine oxidase inhibitors (IMAOs) (bifemelane, hydracarbazine, isocarboxazid, moclobemide,

nialamide, phenelzine, pirlindole, rasagiline, safinamide, selegiline, toloxatane and tranylcypromine); tricyclics (TCAs) and tetracyclics (TeCAs) (amitriptyline, amoxapine, clomipramine, desipramine, doxepine, imipramine, maprotiline, nortriptyline, protriptyline and trimipramine); selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline); serotonin-noradrenaline reuptake inhibitors (SNRIs) (desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine); serotonin partial agonist and reuptake inhibitors (SPARIs) (nefazodone, trazodone and milazodone); noradrenergic and specific serotoninergic antidepressants (NASSAs) (mianserin and mirtazapine); noradrenaline reuptake inhibitors (NRIs) (reboxetine); noradrenaline and dopamine reuptake inhibitors (NDRIs) (buproprion); others (agomelatine, esketamine, S-adenosyl-methionine and vortioxetine). The category of antipsychotics included two classes: first-generation antipsychotics (FGAs) (chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, promazine and trifluoperazine) and second-generation antipsychotics (SGAs) (amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone). Anti-ADHD medications included psychostimulants (d-amphetamine, lisdexamphetamine and methylphenidate) and medications with other mechanisms (atomoxetine, clonidine, guanfacine and modafinil). Mood stabilizers included antiepileptics (carbamazepine, gabapentin, lamotrigine, pregabalin, oxcarbazepine, topiramate and valproate) and lithium.

Primary and secondary outcomes

The primary outcome was the safety/coverage ratio (i.e., the number of adverse events significantly worse than placebo/no treatment over the number of adverse events covered by literature) for those psychotropic medications for which ≥20% of the 78 *a priori* selected events were covered by the literature. The secondary outcomes were the list of adverse events associated with each medication, their effect size ± 95% CI, and the study quality.

The magnitude of associations of each medication with the main adverse events was classified as small (≤0.5), medium (between >0.5 and <0.8) and large (≥0.8) for continuous outcomes (effect sizes >0) and inverse thresholds for effect sizes <0. For categorical outcomes, the magnitude of associations was classified as small (<3), medium (between ≥3 and <5) and large (≥5) for equivalent odds ratios (eORs) >1, and reciprocal thresholds for eORs <1[43].

Quality of evidence

The quality of MAs and NMAs was measured with a modified version of the A Measurement Tool for the Assessment of Multiple Systematic Reviews (AMSTAR)-PLUS[44], which allows to measure both the quality of the methodology of (N)MAs, and the quality of the studies included in (N)MAs (AMSTAR-Content). AMSTAR quality was considered low when the final score was <4, medium when it was 4-7, and high when >7[45]. For AMSTAR-Content, quality was considered low when the final score was <4, medium when it was 4-6, and high when >6. The overall quality of (N)MAs was rated choosing the lower score of either AMSTAR or AMSTAR-Content.

The quality of RCTs was assessed with the Risk of Bias tool 2[46], assigning high risk, low risk, or some concerns. The quality of cohort studies was measured with the Newcastle-Ottawa Scale (NOS)[47], and high quality was assigned when the NOS score was ≥7.

Statistical analysis

We extracted random effects effect sizes ± 95% CIs for the difference in the incidence of specific adverse events between individual medications and placebo (RTCs), or between treated vs. untreated youth with mental disorders (cohort studies). We considered ORs, log ORs or risk ratios (RRs) with respective numbers-needed-to-harm (NNH) for categorical outcomes, and standardized mean differences (SMDs) or mean differences (MDs) for continuous outcomes.

We calculated the overall proportional coverage of the *a priori* selected adverse events for each of the individual psychotropic medications using descriptive statistics, and divided the covered adverse events into those with and without significantly higher frequencies vs. placebo or matched subjects. Furthermore, we identified medications with the best or worst safety/coverage ratio among those that had results for ≥20% of the adverse events.

RESULTS

Search results

The flow chart of the search process for the three systematic searches is presented in Figure 1. At title and abstract level, we screened 1,309 hits for NMAs and MAs, 5,716 hits for individual RCTs and 8,518 hits for cohort studies. We assessed full texts of 292 articles for NMAs and MAs, 519 for individual RCTs, and 173 for cohort studies. We ultimately extracted data from nine NMAs, 39 MAs, 90 individual RCTs, and eight cohort studies, including 337,686 children and adolescents (120,637 for antidepressants, 66,764 for antipsychotics, 148,664 for anti-ADHD medications, and 1,621 for mood stabilizers).

For antidepressants, we included four NMAs[40,48-50], 15 MAs[36,51-64], 27 individual RCTs[65-91] also covered in those NMA/MAs, six additional RCTs[92-97], and three cohort studies[98-100]. There were 120,637 youth on antidepressants, including 24,659 across 139 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (22,704 in NMA/MAs, 1,955 in additional RCTs), and 95,978 in three cohort studies.

For antipsychotics, we included three NMAs[101-103], 11 MAs[104-114],

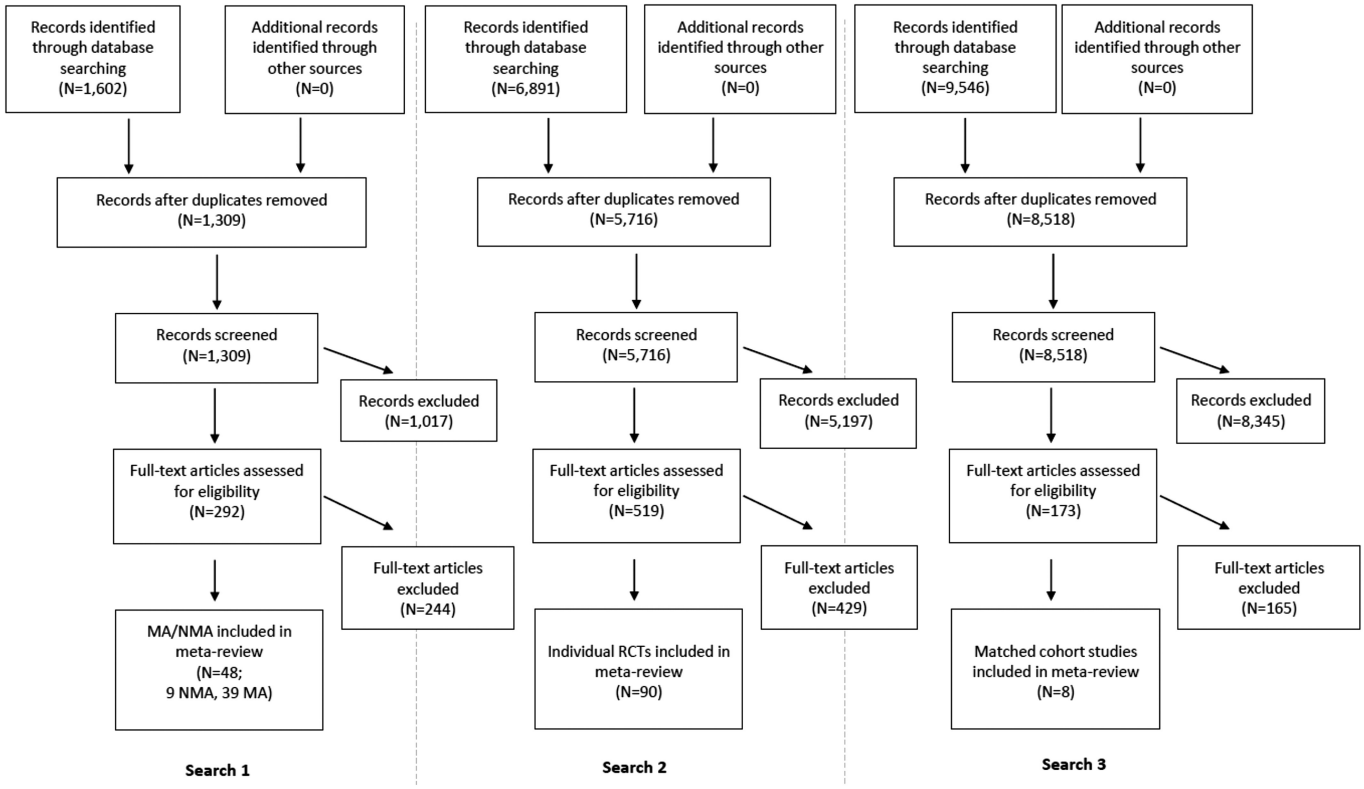

Figure 1 PRISMA flow chart for inclusion of studies. Search 1: network meta-analyses (NMA) and meta-analyses (MA); Search 2: individual randomized controlled trials (RCTs); Search 3: cohort studies controlling for confounding by indication

25 individual RCTs[115-139] also included in those NMA/MAs, three additional RCTs[140-142], and two cohort studies[99,143]. There were 66,764 youth on antipsychotics, including 7,712 across 53 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (6,725 in NMA/MAs, 987 in additional RCTs), and 59,052 in two cohort studies.

For anti-ADHD medications, we included three NMAs[49,144,145], 11 MAs[146-156], 12 RCTs[157-168] also included in those NMA/MAs, five additional RCTs[169-173], and five cohort studies[99,174-177]. There were 148,664 youth on anti-ADHD medications, including 28,834 across 298 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (27,188 in NMA/MAs, 1,646 in additional RCTs), and 119,830 in five cohort studies.

For mood stabilizers, we included four MAs[107,112,178,179], seven RCTs[180-186] also included in those NMA/MAs, and five additional RCTs[187-191]. There were 1,621 youth across 23 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (1,244 in NMA/MA, 377 in additional RCTs).

Quality of included evidence

Among nine NMAs, the median AMSTAR score was 10 (interquartile range, IQR=9-11) and the median AMSTAR-Content score was 5 (IQR=5-7). The quality was moderate in two (22.2%) NMAs, and high in the remaining seven NMAs (77.8%). The RCTs included in NMAs had moderate quality in six (66.7%) NMAs, and high quality in three (33.3%). The overall quality of the evidence from included NMAs was moderate in six (66.7%) and high in three (33.3%).

Among 39 MAs, the median AMSTAR score was 9 (IQR=7-10) and the median AMSTAR-Content was 5 (IQR=4-6). The quality was moderate in 11 MAs (28.2%), and high in the remaining 28 (71.8%). The RCTs included in MAs had low quality in nine (23.1%) MAs, moderate quality in 23 (59.0%), and high in seven (17.9%). The overall quality of the evidence from included MAs was low in nine (23.1%), moderate in 25 (64.1%) and high in five (12.8%).

Among 90 individual RCTs, 26 (28.6%) had high risk of bias, 43 (47.3%) raised some concerns, and 22 (24.2%) had low risk of bias.

Among eight cohort studies, six (75%) had a high quality according to the Newcastle-Ottawa scale, and the median quality score was 7 (IQR=7-8).

Overall safety of classes of psychotropic medications in children and adolescents with mental disorders

Antidepressants

Out of 44 antidepressants, 18 (40.9%) had adverse event data covered in the literature. The available antidepressant literature covered 0-24.4% (mean: 5.6%, median: 0%) of the reviewed adverse events. Details on the proportion of the 78 adverse events covered in the literature and of the adverse events that were sig-

nificantly worse with individual antidepressants vs. placebo/controls are reported in Table 1 and Figure 2.

Among antidepressants with ≥20% of adverse events covered, the safety/coverage ratio was the best for escitalopram (1/17 adverse events covered significantly worse) and fluoxetine (1/16), progressively decreasing through vilazodone (2/16), paroxetine (3/16), sertraline (4/19), to venlafaxine, which had the worst safety/coverage ratio (7/16).

Five antidepressants were associated with significantly worse nausea/vomiting (duloxetine, nefazodone, paroxetine, sertraline, vilazodone), four with discontinuation due to adverse event (duloxetine, imipramine, venlafaxine, vilazodone), three with any extrapyramidal side effect (clomipramine, imipramine, paroxetine), two each with sedation (imipramine, nefazodone), diarrhea (duloxetine, sertraline), headache (nefazodone, venlafaxine), anorexia (amitriptyline, venlafaxine), and weight gain/increased body mass index (escitalopram, sertraline), and one each with weight loss (fluoxetine), and suicidality (venlafaxine).

Antipsychotics

Out of 21 antipsychotics, 15 (71.4%) had adverse event data covered in literature. The antipsychotic literature covered a range of 0-56.4% (mean: 16.6%, median: 2.6%) of the reviewed adverse events. Details of the proportion of the 78 adverse events covered in the literature and of adverse events that were significantly worse with individual antipsychotics vs. placebo/controls are reported in Table 2 and Figure 2.

Among antipsychotics with ≥20% of adverse events covered, lurasidone had the best safety/coverage ratio (1/33 covered adverse events significantly worse), progressively decreasing through asenapine (2/22), quetiapine (5/37), ziprasidone (4/25), paliperidone (5/26), risperidone (12/44), aripiprazole (10/35), to olanzapine, which had the worst safety/coverage ratio (13/25).

Ten antipsychotics were associated with significantly worse sedation (aripiprazole, clozapine, haloperidol, loxapine, molindone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone), nine with any extrapyramidal side effect (amisulpride, aripiprazole, haloperidol, loxapine, molindone, olanzapine, paliperidone, risperidone, ziprasidone), seven with weight gain/increased body mass index (aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, risperidone), five with hyperprolactinemia (haloperidol, olanzapine, paliperidone, quetiapine, risperidone), and three each with increased cholesterol (aripiprazole, olanzapine, quetiapine) and glucose increase/diabetes (asenapine, olanzapine, risperidone).

Anti-ADHD medications

All seven anti-ADHD medications had adverse event data covered in the literature. The available literature covered 7.7-32.1% (mean: 19.0%, median: 17.9%) of the reviewed adverse events. Details of the proportion of the 78 adverse events covered in the literature and of adverse events that were significantly worse with individual anti-ADHD medications vs. placebo/controls are reported in Table 3 and Figure 2.

Among anti-ADHD medications with ≥20% of adverse events covered, methylphenidate had the best safety/coverage ratio (5/25 adverse events covered significantly worse), while guanfacine and atomoxetine had the worst safety/coverage ratio (4/16 and 5/20, respectively).

Five anti-ADHD medications were associated with significantly worse anorexia (atomoxetine, d-amphetamine, lisdexamphetamine, methylphenidate, modafinil), four with insomnia (d-amphetamine, lisdexamphetamine, methylphenidate, modafinil), three with weight loss (atomoxetine, methylphenidate, modafinil), two each with abdominal pain (methylphenidate, guanfacine), discontinuation due to adverse event (lisdexamphetamine, guanfacine), hypertension (atomoxetine, lisdexamphetamine), and sedation (clonidine, guanfacine), and one with QT prolongation (guanfacine).

Mood stabilizers

Out of eight mood stabilizers, six (75.0%) had adverse event data covered in the literature. The mood stabilizer literature covered 0-24.4% (mean: 12.7%, median: 14.1%) of the reviewed adverse events. Details on the proportion of the 78 adverse events covered in the literature and of adverse events that were worse with individual mood stabilizers vs. placebo/controls are reported in Table 4 and Figure 2.

Among mood stabilizers with ≥20% of adverse events covered, the best safety/coverage ratio emerged for lithium (0/16 adverse events covered significantly worse), while valproate showed the worst safety/coverage ratio (4/19).

Two mood stabilizers were associated with significantly worse sedation (oxcarbazepine, valproate), and weight gain/increased body mass index (oxcarbazepine, valproate), and one each with weight loss or anorexia (topiramate), thrombocytopenia and leucocytopenia (valproate), and nausea/vomiting (oxcarbazepine).

Evidence from studies lasting ≥6 months

For antidepressants, no RCT lasted ≥6 months, while one cohort studies lasted 6 to 12 months[100], and two ≥12 months (range: 12-130 months)[98,99]. Significant associations emerged between current mixed antidepressants and fractures (small effect size, ≥12 months), but this association became non-significant when considering past exposure to antidepressants. Also, while antidepressants had a small association (≥12 months) with increased risk of any cancer in the first version of the analyses from a large cohort study, additional analyses from the same database did not confirm such association when removing mixed medications[99].

For antipsychotics, no RCT lasted ≥6 months, no cohort study lasted 6-12 months, while two cohort studies lasted ≥12 months (range: 84-130 months)[99,143]. A large association was found be-

Table 1 Safety of antidepressants in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed antidepressants	12 (15.4%)	6 (7.7%)	Anorexia[48]	OR	4.01	1.63-10.17	NMA	M	26,114
			Discontinuation due to adverse event[59]	RR	1.66	1.20-2.28	MA	M	6,778
			Fractures[98]	HR	1.03	1.00-1.06	C	H	50,673
			Insomnia[63]	RR	2.16	1.42-3.27	MA	M	1,500
			Nausea/vomiting[63]	RR	1.88	1.44-2.45	MA	M	2,101
			Suicidality[56]	RR	1.95	1.28-2.98	MA	M	3,930
Mixed serotonin-noradrenaline reuptake inhibitors	9 (11.5%)	3 (3.8%)	Headache[63]	RR	1.52	1.09-2.13	MA	M	688
			Nausea/vomiting[63]	RR	1.97	1.36-2.87	MA	M	688
			Serious adverse events[59]	RR	2.10	1.19-3.69	MA	M	NA
Mixed selective serotonin reuptake inhibitors	14 (17.9%)	4 (5.1%)	Discontinuation due to adverse event[49]	Log OR	–1.8	–3.4 to –0.4	NMA	H	2,623
			Headache[63]	RR	1.27	1.03-1.56	MA	M	2,297
			Nausea/vomiting[63]	OR	1.89	1.42-2.52	MA	M	831
			Serious adverse events[59]	RR	1.72	1.12-2.63	MA	M	NA
Mixed tricyclics	12 (15.4%)	4 (5.1%)	Dry mouth[63]	RR	3.28	1.82-5.90	MA	M	232
			Hypotension[64]	OR	6.78	2.06-22.26	MA	L	324
			Tremor[64]	OR	6.29	1.78-22.17	MA	L	308
			Suicidality[49]	Log OR	25.1	4.5-57.4	NMA	H	2,623
Amitriptiyline	2 (2.6%)	1 (1.3%)	Anorexia[65]	NA	Sig	Sig	RCT	M	31
Bupropion	8 (10.3%)	0 (0.0%)							
Citalopram	8 (10.3%)	0 (0.0%)							
Clomipramine	8 (10.3%)	1 (1.3%)	Any extrapyramidal side effects[97]	RR	9.35	1.28-68.6	RCT	M	60
Desipramine	6 (7.7%)	0 (0.0%)							
Desvenlafaxine	9 (11.5%)	0 (0.0%)							
Duloxetine	13 (16.7%)	3 (3.8%)	Diarrhea[93]	OR	3.26	1.09-9.71	RCT	H	556
			Discontinuation due to adverse event[40]	OR	2.80	1.20-9.42	NMA	H	5,260
			Nausea/vomiting[93]	OR	1.93	1.15-3.25	RCT	H	556
Escitalopram	17 (21.8%)	1 (1.3%)	Weight gain[87]	OR	2.30	1.01-5.25	RCT	L	312
Fluoxetine	16 (20.5%)	1 (1.3%)	Weight loss[79]	MD	–1.2	–1.85 to –0.55	RCT	M	103

Table 1 Safety of antidepressants in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls) *(continued)*

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Fluvoxamine	11 (14.1%)	1 (1.3%)	Abdominal pain[89]	RR	1.70	1.06-2.71	RCT	M	128
Imipramine	15 (19.2%)	5 (6.4%)	Any extrapyramidal side effects[90]	OR	7.35	1.62-33.3	RCT	M	182
			Discontinuation due to adverse event[40]	OR	5.49	1.96-20.9	NMA	H	5,260
			Dry mouth[62]	RR	3.81	1.25-11.6	MA	M	56
			Hypotension[90]	OR	13.6	1.74-107	RCT	M	182
			Sedation[90]	OR	4.44	1.22-16.2	RCT	M	182
Mirtazapine	2 (2.6%)	0 (0.0%)							
Nefazodone	8 (10.3%)	3 (3.8%)	Headache[91]	NA	Sig	Sig	RCT	L	528
			Nausea/vomiting[91]	NA	Sig	Sig	RCT	L	528
			Sedation[91]	NA	Sig	Sig	RCT	L	528
Nortriptyline	3 (3.8%)	1 (1.3%)	Hypertension[67]	NA	Sig	Sig	RCT	M	50
Paroxetine	16 (20.5%)	3 (3.8%)	Any extrapyramidal side effects[90]	OR	5.12	1.09-24.1	RCT	M	180
			Insomnia[82]	OR	2.68	1.20-6.00	RCT	M	319
			Nausea/vomiting[69]	OR	3.69	1.01-13.5	RCT	L	319
Sertraline	19 (24.4%)	4 (5.1%)	Diarrhea[68]	OR	3.04	1.25-7.38	RCT	H	376
			Insomnia[84]	OR	4.05	1.94-8.49	RCT	L	189
			Nausea/vomiting[68]	OR	2.65	1.03-6.77	RCT	H	189
			Weight gain[68]	NA	Sig	Sig	RCT	H	376
Venlafaxine	16 (20.5%)	7 (9.0%)	Abdominal pain[70]	OR	2.36	1.29-4.32	RCT	M	367
			Anorexia[72]	OR	4.25	1.55-11.63	RCT	M	323
			Discontinuation due to adverse event[40]	OR	3.19	1.01-18.70	NMA	H	5,260
			Headache[72]	OR	0.56	0.35-0.92	RCT	M	313
			Hypertension[70]	NA	Sig	Sig	RCT	M	367
			Serious adverse events[70]	OR	4.14	1.15-14.9	RCT	M	367
			Suicidality[40]	OR	0.13	0.00-0.55	NMA	H	5,260
Vilazodone	16 (20.5%)	2 (2.6%)	Discontinuation due to adverse event[94]	OR	8.55	1.13-64.8	RCT	H	526
			Nausea/vomiting[94]	OR	4.40	2.43-9.76	RCT	H	526

OR – odds ratio, RR – risk ratio, Log OR – log odds ratio, HR – hazard ratio, MD – mean difference, NMA – network meta-analysis, MA – meta-analysis, RCT – randomized controlled trial, C – cohort study, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

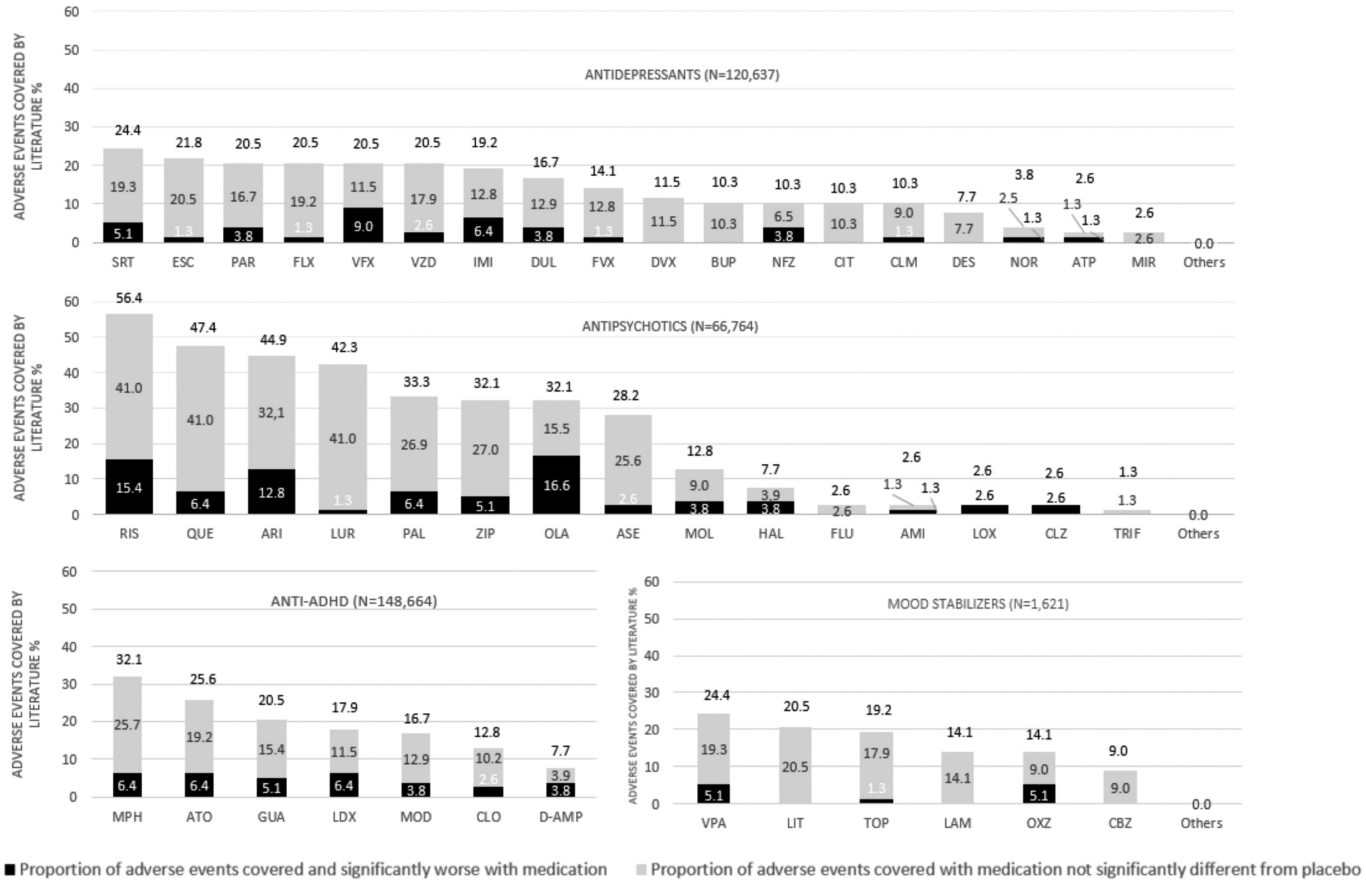

Figure 2 Proportion of adverse events covered by the literature that were significantly worse or non-significantly different from placebo, for antidepressants, antipsychotics, anti-attention-deficit/hyperactivity (ADHD) medications, and mood stabilizers in children and adolescents with mental illness. AMI – amisulpride, ATP – amitriptyline, ARI – aripiprazole, ASE – asenapine, ATO – atomoxetine, BUP – bupropion, CBZ – carbamazepine, CIT – citalopram, CLM – clomipramine, CLO – clonidine, CLZ – clozapine, DES – desipramine, DVX – desvenlafaxine, D-AMP – d-amphetamine, DUL – duloxetine, ESC – escitalopram, FLX – fluoxetine, FLU – fluphenazine, FVX – fluvoxamine, GUA – guanfacine, HAL – haloperidol, IMI – imipramine, LAM – lamotrigine, LIT – lithium, LDX – lisdexamphetamine, LOX – loxapine, LUR – lurasidone, MPH – methylphenidate, MIR – mirtazapine, MOD – modafinil, MOL – molindone, NFZ – nefazodone, NOR – nortriptyline, OLA – olanzapine, OXZ – oxcarbazepine, PAL – paliperidone, PAR – paroxetine, QUE – quetiapine, RIS – risperidone, SRT – sertraline, TOP – topiramate, TRIF – trifluoperazine, VPA – valproate, VFX – venlafaxine, VZD – vilazodone, ZIP – ziprasidone

tween mixed SGAs and diabetes (≥12 months).

For anti-ADHD medications, no RCT lasted ≥6 months, no cohort study 6-12 months, while five cohort studies lasted ≥12 months (range: 12-130 months)[99,174-177]. A large protective association was found between methylphenidate and any cancer (≥12 months), which survived after additional analyses from the same database removing mixed medications[99].

For mood stabilizers, no RCT lasted ≥6 months and no cohort studies were identified, so there was no long-term data on adverse events for any mood stabilizer.

DISCUSSION

This meta-review of 80 psychotropic medications summarized data on 78 preselected adverse events in children and adolescents with mental illness, quantifying data for 18 antidepressants (N=120,637), 15 antipsychotics (N=66,764), seven anti-ADHD medications (N=148,664) and six mood stabilizers (N=1,621).

Overall, the amount of coverage of the preselected adverse events was 0-24.4% for antidepressants (no data for 26 antidepressants), 0-56.4% for antipsychotics (no data for six antipsychotics), 7.7-32.1% for anti-ADHD medications (data for all anti-ADHD medications), and 0-24.4% for mood stabilizers (no data for two mood stabilizers).

Data were reported on ≥20% of the preselected adverse events for only six antidepressants (sertraline, escitalopram, paroxetine, fluoxetine, venlafaxine, vilazodone), eight antipsychotics (risperidone, quetiapine, aripiprazole, lurasidone, paliperidone, ziprasidone, olanzapine, asenapine), three anti-ADHD medications (methylphenidate, atomoxetine, guanfacine), and two mood stabilizers (valproic acid, lithium).

Thus, the present meta-review shows that the evidence on ad-

Table 2 Safety of antipsychotics in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed antipsychotics	3 (3.8%)	2 (2.6%)	Discontinuation due to adverse event[104]	RR	2.40	1.10-5.30	MA	M	942
			Weight gain[104]	SMD	0.60	0.30-0.90	MA	M	625
Mixed second-generation antipsychotics	17 (21.8%)	10 (12.8%)	Akathisia[107]	NNH	20.4	14.1-36.5	MA	M	1,118
			Any extrapyramidal side effects[107]	NNH	7.5	5.7-11.0	MA	M	1,118
			Diabetes[143]	IRR	10.5	2.06-33.2	C	H	37,866
			Discontinuation due to adverse event[107]	NNH	20.4	13.4-47.5	MA	M	1,118
			Dystonia[105]	OR	3.90	1.70-8.40	MA	M	666
			Hyperprolactinemia[107]	NNH	7.9	6.10-11.1	MA	M	1,118
			Sedation[107]	NNH	4.7	3.90-6.0	MA	M	1,118
			Tardive dyskinesia[105]	OR	3.90	1.10-14.1	MA	M	666
			Tremor[105]	OR	3.49	1.50-8.0	MA	M	666
			Weight gain[107]	NNH	10.0	7.50-14.8	MA	M	1,118
Amisulpride	2 (2.6%)	1 (1.3%)	Any extrapyramidal side effects[124]	OR	9.60	1.48-62	RCT	L	27
Aripiprazole	35 (44.9%)	10 (12.8%)	Akathisia[102]	OR	3.10	1.0-9.0	NMA	M	2,158
			Any extrapyramidal side effects[103]	OR	3.80	2.20-6.20	NMA	M	3,258
				NNH	4.1	3.1-6.2	MA	M	296
			Asthenia[109]	OR	8.54	2.59-28.1	MA	M	405
			Anorexia[109]	OR	5.11	1.14-23.0	MA	M	308
			Increased cholesterol[108]	RR	2.50	1.40-4.40	MA	L	120
			Fever[109]	OR	5.89	1.23-28.2	MA	M	308
			Sedation[103]	OR	6.10	2.80-12.2	NMA	M	3,348
			Sialorrhea[109]	OR	10.5	1.30-84.2	MA	M	314
			Tremor[109]	OR	11.5	1.40-91.6	MA	M	313
			Weight gain[103]	OR	4.40	2.0-8.90	NMA	M	3,401
Asenapine	22 (28.2%)	2 (2.6%)	Increased body mass index[136]	NA	Sig	Sig	RCT	M	306
			Increased glucose[141]	NA	Sig	Sig	RCT	M	403
Clozapine	2 (2.6%)	2 (2.6%)	Sedation[103]	OR	54.8	3.9-260	NMA	M	3,348
			Weight gain[101,103]	OR	13.8	2.20-49.2	NMA	M	3,401
				SMD	–0.92	–1.61 to –0.22	NMA	M	3,003

Table 2 Safety of antipsychotics in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls) *(continued)*

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Fluphenazine	2 (2.6%)	0 (0.0%)							
Haloperidol	6 (7.7%)	3 (3.8%)	Any extrapyramidal side effects[131]	OR	59.1	6.66-525	RCT	L	50
			Hyperprolactinemia[101]	SMD	1.0	0.2-1.8	NMA	M	3,003
			Sedation[101]	Log OR	–1.3	–2.3 to –0.3	NMA	M	3,003
Loxapine	2 (2.6%)	2 (2.6%)	Any extrapyramidal side effects[131]	OR	62.4	7.05-553	RCT	L	50
			Sedation[101]	Log OR	–1.9	–3.1 to – 0.7	NMA	M	3,003
Lurasidone	33 (42.3%)	1 (1.3%)	Nausea/vomiting[142]	OR	3.1	1.50-6.60	RCT	M	343
Molindone	10 (12.8%)	3 (3.8%)	Akathisia[102]	OR	24.1	5.70-102	NMA	M	2,158
			Any extrapyramidal side effects[102]	OR	10.4	3.0-35.6	NMA	M	2,158
			Sedation[102]	OR	10.9	2.40-50.2	NMA	M	2,158
Olanzapine	25 (32.1%)	13 (16.6%)	Akathisia[102]	OR	3.70	1.10-12.7	NMA	M	2,158
			Anemia[119]	NA	Sig	Sig	RCT	L	107
			Any extrapyramidal side effects[103]	OR	6.40	2.40-13.8	NMA	M	3,258
			Increased cholesterol[103]	MD	4.5	1.2-7.7	NMA	M	1,784
			Increased creatine phosphokinase[119]	NA	Sig	Sig	RCT	L	107
			Increased glucose[103]	MD	2.1	0.1-4.3	NMA	M	1,784
			Hyperprolactinemia[101,103]	OR	15.6	4.40-41.1	NMA	M	3,348
				SMD	0.7	0.3-1.1	NMA	M	3,003
			Hypertension[130]	NA	Sig	Sig	RCT	L	107
			Liver damage[113]	OR	18.7	3.60-96.4	MA	H	265
			Sexual adverse events[108]	MD	11.5	8.80-14.1	MA	L	241
			Sedation[103]	OR	8.50	4.0-16.6	NMA	M	3,348
			Increased triglycerides[103,113]	OR	5.10	2.80-9.40	MA	M	268
				MD	20.2	9.8-30.5	NMA	H	1,655
			Weight gain[103]	OR	15.1	6.60-31.1	NMA	M	3,401
Paliperidone	26 (33.3%)	5 (6.4%)	Akathisia[102]	OR	5.60	1.80-17.7	NMA	M	2,158
			Any extrapyramidal side effects[102]	OR	6.30	2.30-16.8	NMA	M	2,158
			Hyperprolactinemia[101]	SMD	0.61	0.35-0.86	NMA	M	3,003
			Sedation[101]	Log OR	–2.4	–4.4 to –0.3	NMA	M	3,003
			Weight gain[101]	SMD	–0.7	–1.0 to –0.5	NMA	M	3,003

Table 2 Safety of antipsychotics in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls) *(continued)*

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Quetiapine	37 (47.4%)	5 (6.4%)	Increased cholesterol[103]	MD	10.8	6.6-145	NMA	M	1,784
			Hyperprolactinemia[101]	SMD	0.4	0.1-0.7	NMA	M	3,003
			Sedation[103]	OR	5.40	2.90-9.30	NMA	M	3,348
			Increased triglycerides[103]	MD	19.5	11.8-27.2	NMA	M	1,655
			Weight gain[101,103]	OR	6.20	2.60-13.6	NMA	M	3,401
				SMD	–0.85	–1.09 to –0.61	NMA	M	3,003
Risperidone	44 (56.4%)	12 (15.4%)	Akathisia[102]	OR	4.0	1.40-10.9	NMA	M	2,158
			Any extrapyramidal side effects[103]	OR	3.70	2.20-6.0	NMA	M	3,258
			Asthenia[109]	OR	3.89	1.77-8.53	MA	M	179
			Constipation[109]	OR	3.42	1.33-8.80	MA	M	179
			Gastrointestinal symptoms[115]	OR	3.74	1.15-12.2	RCT	H	168
			Increased glucose[103]	MD	3.70	1.10-6.40	NMA	M	1,784
			Hyperprolactinemia[101,103]	OR	38.6	8.60-126	NMA	M	1,180
				SMD	1.40	0.80-2.0	NMA	M	3,003
			Increased appetite[109]	OR	4.82	2.35-9.88	MA	M	179
			Nasopharyngitis/upper respiratory tract infection[109]	OR	3.14	1.26-7.80	MA	M	179
			Sedation[103]	OR	7.30	4.60-11.2	NMA	M	3,348
			Tachycardia[109]	OR	6.87	1.49-31.7	MA	M	179
			Weight gain[101,103]	OR	6.0	3.0-11.0	NMA	M	3,401
				SMD	–0.61	–0.89 to –0.32	NMA	M	3,003
Trifluoperazine	1 (1.3%)	0 (0.0%)							
Ziprasidone	25 (32.1%)	4 (5.1%)	Any extrapyramidal side effects[103]	OR	20.6	3.50-69.0	NMA	M	3,258
			Dizziness[135]	OR	9.15	1.20-69.7	RCT	L	283
			Nausea/vomiting[135]	OR	4.80	1.10-21.1	RCT	L	283
			Sedation[103]	OR	8.70	2.70 -22.0	NMA	M	3,348

OR – odds ratio, RR – risk ratio, Log OR – log odds ratio, SMD – standardized mean difference, IRR – incidence rate ratio, NNH – number needed to harm, NMA – network meta-analysis, MA – meta-analysis, RCT – randomized controlled trial, C – cohort study, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

Table 3 Safety of anti-attention-deficit/hyperactivity (ADHD) medications in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed anti-ADHD medications	19 (24.4%)	7 (9.0%)	Abdominal pain[155]	RR	1.44	1.03-2.00	MA	H	2,155
			Anorexia[155]	RR	6.31	2.58-15.5	MA	H	2,467
			Discontinuation due to adverse event[144]	OR	2.30	1.36-3.89	NMA	H	14,346
			Hypertension[144]	SMD	0.09	0.01-0.18	NMA	H	14,346
			Insomnia[155]	RR	3.80	2.12-6.83	MA	H	2,429
			Nausea/vomiting[155]	RR	1.63	1.04-2.56	MA	H	1,579
			Weight loss[144]	SMD	–0.71	–1.15 to –0.27	NMA	H	14,346
Mixed α-2 agonists	5 (6.4%)	1 (1.3%)	Discontinuation due to adverse event[49]	Log OR	–29.6	–95.5 to –2.6	NMA	M	2,623
Atomoxetine	20 (25.6%)	5 (6.4%)	Anorexia[147]	RR	2.51	1.77-3.57	MA	M	2,179
			Gastrointestinal symptoms[147]	RR	1.76	1.51-2.07	MA	M	3,712
			Hypertension[144]	SMD	0.12	0.02-0.22	NMA	H	14,346
			Nausea/vomiting[156]	RR	1.91	1.24-2.94	MA	L	193
			Weight loss[144]	SMD	–0.84	–1.16 to –0.52	NMA	H	14,346
Clonidine	10 (12.8%)	2 (2.6%)	Hypotension[149]	Hedges' g	0.52	0.15-0.89	MA	M	119
			Sedation[164]	OR	7.67	2.92-20.1	RCT	M	230
d-amphetamine	6 (7.7%)	3 (3.8%)	Anorexia[170]	NA	Sig	Sig	RCT	L	81
			Insomnia[170]	NA	Sig	Sig	RCT	L	81
			Irritability[170]	NA	Sig	Sig	RCT	L	81
Guanfacine	16 (20.5%)	4 (5.1%)	Abdominal pain[166]	OR	4.51	1.34-15.2	RCT	M	455
			Discontinuation due to adverse event[144]	OR	2.64	1.20-5.81	NMA	H	14,346
			QT prolongation[149]	Hedges' g	0.33	0.12-0.54	MA	M	785
			Sedation[149]	RR	2.43	1.06-5.58	MA	M	1,059
Lisdexamphetamine	14 (17.9%)	5 (6.4%)	Anorexia[155]	RR	9.83	5.08-19.0	MA	H	1,081
			Discontinuation due to adverse event[145]	RR	3.11	1.20-3.76	NMA	M	6,931
			Dry mouth[169]	OR	8.63	1.13-66.0	RCT	H	547
			Hypertension[144]	SMD	0.14	0.03-0.25	NMA	H	14,346
			Insomnia[155]	RR	5.91	2.84-12.3	MA	H	1,081
Methylphenidate	25 (32.1%)	5 (6.4%)	Abdominal pain[154]	RR	1.50	1.26-1.79	MA	M	5,983
			Anorexia[154]	RR	3.21	2.61-3.94	MA	M	5,983
			Insomnia[148]	OR	4.66	1.99-10.9	MA	M	749
			Nausea/vomiting[154]	RR	1.38	1.04-1.84	MA	M	2,630
			Weight loss[144]	SMD	–0.77	–1.09 to –0.45	NMA	H	14,346
Modafinil	13 (16.7%)	3 (3.8%)	Anorexia[153]	RR	5.02	2.55-9.89	MA	M	921
			Insomnia[153]	RR	6.16	3.40-11.2	MA	M	921
			Weight loss[144]	SMD	–0.93	–1.59 to –0.26	NMA	H	14,346

OR – odds ratio, RR – risk ratio, Log OR – log odds ratio, SMD – standardized mean difference, NMA – network meta-analysis, MA – meta-analysis, RCT – randomized controlled trial, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

Table 4 Safety of mood stabilizers in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed mood stabilizers	4 (5.1%)	1 (1.3%)	Sedation[107]	NNH	9.5	6.3-23.5	MA	L	469
Carbamazepine	7 (9.0%)	0 (0.0%)							
Lamotrigine	11 (14.1%)	0 (0.0%)							
Lithium	16 (20.5%)	0 (0.0%)							
Oxcarbazepine	11 (14.1%)	4 (5.1%)	Discontinuation due to adverse event[181]	OR	6.19	1.31-29.3	RCT	M	116
			Nausea/vomiting[181]	OR	3.66	1.33-10.1	RCT	M	116
			Sedation[181]	OR	6.89	1.47-32.4	RCT	M	116
			Weight gain[181]	NA	Sig	Sig	RCT	M	116
Topiramate	15 (19.2%)	1 (1.3%)	Anorexia[182]	OR	21.7	1.19-398	RCT	M	56
Valproate	19 (24.4%)	4 (5.1%)	Leukocytopenia[180]	NA	Sig	Sig	RCT	H	150
			Sedation[107]	NNH	7.8	5.3-15.0	MA	L	231
			Thrombocytopenia[180]	NA	Sig	Sig	RCT	H	150
			Weight gain[107]	Effect size	0.4	0.07-0.73	MA	L	231

OR – odds ratio, RR – risk ratio, NNH – number needed to harm, MA – meta-analysis, RCT – randomized controlled trial, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

verse events of psychotropic medications in children and adolescents is modest overall, and that psychostimulants are the drugs which have been most studied up to now.

The main adverse events for antidepressants were (in descending order of number of medications associated with the specific event): nausea/vomiting, discontinuation due to adverse event, extrapyramidal side effects, weight gain, sedation, diarrhea, headache and anorexia. Based on the safety/coverage ratio among agents with ≥20% adverse event coverage, the safest profile emerged for escitalopram and fluoxetine, and the worst for venlafaxine. These data confirm, and put in a more comprehensive framework, the findings of a previous NMA on antidepressants in children and adolescents[40] (focusing, however, on efficacy as its primary outcome), which showed that both fluoxetine and escitalopram were not associated with more drop-outs than placebo, while venlafaxine was, with a moderate effect size (OR=3.19). In the same NMA, fluoxetine was found to be the only antidepressant significantly superior to placebo with respect to its impact on depressive symptoms (SMD=–0.51). Merging the safety results of the present meta-review with the available evidence on efficacy from that NMA[40], fluoxetine probably has the best harm-benefit ratio among all antidepressants for youth, and might be proposed as the first-line treatment for depressive disorders in children and adolescents.

The main adverse events for antipsychotics were (in descending order of number of medications associated with the specific event): sedation, extrapyramidal side effects, weight gain, hyperprolactinemia, increased cholesterol, and glucose increase. Based on the safety/coverage ratio among agents with ≥20% adverse event coverage, the safest profile emerged for lurasidone, and the worst for olanzapine. These data confirm in part, and put in a more comprehensive framework, the findings of the largest NMA of antipsychotics in children and adolescents with schizophrenia[101] (which, however, focused on efficacy as primary outcome). In the same NMA, the only antipsychotic superior to all others in terms of efficacy was clozapine, and no further difference emerged among other antipsychotics, except for ziprasidone being inferior to molindone, olanzapine and risperidone, and fluphenazine being inferior to all other antipsychotics.

Merging the safety results of the present meta-review with available evidence on efficacy[101], lurasidone might be proposed as the first-line treatment for schizophrenia spectrum disorders in children and adolescents. Less tolerable yet effective medications can be used as second-line treatments, tailoring the choice to each individual patient's expectations and safety priorities (e.g., sexually active subjects might prefer agents not increasing prolactin). Importantly, clozapine should be considered only for treatment-resistant cases, given the lack of evidence regarding its safety in children and adolescents, and its poor safety profile in adults[192], which can be expected to be similar in children and adolescents, if not worse.

The main adverse events for anti-ADHD medications were (in descending order of number of medications associated with the specific event): anorexia, insomnia, weight loss, abdominal pain, hypertension, and sedation. Based on safety/coverage ratio among agents with ≥20% adverse event coverage, the safest pro-

file emerged for methylphenidate, and the worst for atomoxetine and guanfacine. Our comprehensive meta-review provides a finer-grained insight into the adverse events of anti-ADHD medications, while the largest NMA to date[144] did not reveal differences among these drugs concerning tolerability. Somewhat surprisingly, methylphenidate was also protective against cancer when long follow-up was considered, with such protective association surviving additional analyses excluding mixed medications[99]. Further research is warranted on this protective effect.

Our meta-review shows that both atomoxetine and methylphenidate induce weight loss, consistent with previous findings[144]. Sedation was only observed with the alpha-2 agonists clonidine and guanfacine. Clinically, this effect can sometimes be exploited to counter insomnia, but residual daytime sedation may impair cognitive performance in subjects with ADHD. In terms of efficacy, in the above-mentioned NMA[144], only methylphenidate outperformed placebo (SMD=–0.82) according to teachers' ratings. Moreover, methylphenidate was superior to atomoxetine (SMD=0.22). Considering the available safety and efficacy data, methylphenidate might be considered the first-line treatment for ADHD in children and adolescents.

The main adverse events for mood stabilizers were (with the same number of medications associated with the specific event) sedation and weight gain. Based on the safety/coverage ratio among agents with ≥20% adverse event coverage, the safest event profile emerged for lithium, and the worst for valproate. While the lack of any association between lithium and thyroid/kidney damage[188] as well as weight gain[190] is likely due to the small sample size of the included RCTs (N=124 and N=31, respectively), and the short duration of one RCT (3 months)[188], significant lithium-induced weight gain would have emerged during the six-month RCT[190]. Considering the well-established efficacy of lithium, which is the first-line treatment in adolescent bipolar disorder according to international guidelines[193], currently available data on the harm-benefit ratio favor the choice of lithium among mood stabilizers in youth. However, long-term cohort studies in this age group are clearly warranted. All antipsychotics have more adverse events than lithium according to this meta-review, except for lurasidone, which seems to have a comparably safe profile and could be preferred to lithium for the treatment of bipolar depression[193,194].

The results of this meta-review need to be interpreted considering some limitations. First, data for adverse events are lacking for some, and limited for many of the reviewed psychotropic medications. Absence of evidence for certain adverse events cannot be taken as evidence of their absence. Therefore, a more comprehensive reporting of adverse events is strongly recommended in studies concerning the use of psychotropic medications in children and adolescents.

Second, information on adverse events is mostly based on spontaneous reports. While these will underestimate the frequency of such events, the use of rating scales might increase the level of noise. Interviews and/or self-report scales would assure a more comprehensive capturing of adverse events, and applying appropriate thresholds for severity and frequency could enhance the signal-to-noise ratio.

Third, long-term and rare adverse events are likely underrepresented in the reviewed data, that are based mostly on short- and medium-term RCTs, with only eight cohort studies of sufficient methodological quality providing longer-term data. Fourth, we did not differentiate the adverse events based on dose effects due to limited data. Fifth, we took a transdiagnostic approach in order to capture all available information. Although certain adverse events could possibly differ across the various mental disorders, no clear evidence exists for this possibility, and other patient- and medication-related factors that are transdiagnostic (e.g., age, treatment-naiveté, dose, co-medications) are likely much more important than diagnosis.

Of course, safety of medications needs to be considered along with their efficacy. This was not a focus of this large-scale meta-review, but we discussed our findings in the context of efficacy data from the largest and most recent NMA or MA for the respective medication class for its main indication. Finally, this meta-review does not include data on strategies to prevent or mitigate adverse events of psychotropic medications in youth. While this is clearly an important area, this topic is beyond the scope of the present review and needs to be considered on the basis of targeted reviews and studies focusing on specific adverse events of individual medications[195-201].

In summary, the results of this meta-review have several clinical implications, which can guide the use of psychotropic medications in children and adolescents. First, for some medications, there are no or very insufficient high-quality adverse event data in this age group, which should caution their use. Second, within each of the four major classes, we provide a hierarchy of medications on the basis of the available safety evidence: the preferred agents are likely to be fluoxetine and escitalopram among antidepressants, lurasidone among antipsychotics, methylphenidate among anti-ADHD medications, and lithium among mood stabilizers. By contrast, potentially least preferred agents based on safety are likely to be venlafaxine among antidepressants, olanzapine among antipsychotics, atomoxetine and guanfacine among anti-ADHD medications, and valproate among mood stabilizers.

Together with the efficacy data for these medications, the results of this comprehensive and updated meta-review of top-tier evidence regarding the safety of antidepressants, antipsychotics, anti-ADHD medications and mood stabilizers in children and adolescents can inform clinical practice, research and treatment guidelines.

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