COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID DUR REPORT
DECEMBER 2023

ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS:
INDICATIONS AND USE OF MULTIPLE ANTIDEPRESSANTS

Report finalized: November 2023
Report presented: December 2023

Drug Regimen Review Center

Lauren Heath, PharmD, MS, BCACP, Clinical Pharmacist
Tami Haines, BS Pharm, Clinical Pharmacist
Monet Luloh, PharmD, Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Editor
Joanne LaFleur, PharmD, MSPH, Director and Associate Professor

University of Utah College of Pharmacy, Drug Regimen Review Center

CONTENTS

LIST OF TABLES

ABBREVIATIONS

AACAP	American Academy of Child and Adolescent Psychiatry
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
APA	American Psychological Association
BAP	The British Association for Psychopharmacology
CBT	Cognitive behavioral therapy
IPT	Interpersonal therapy
DHHS	Department of Health and Human Services
DMDD	Disruptive mood dysregulation disorder
DNRI	Dopamine-norepinephrine reuptake inhibitor
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision
ECT	Electroconvulsive therapy
FDA	United States Food and Drug Administration
GAD	Generalized anxiety disorder
LOE	Level of evidence
MDD	Major depressive disorder
NICE	The National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
NSSRI	Non-selective serotonin reuptake inhibitor
OCD	Obsessive compulsive disorder
OL	Off-label
SAD	Social anxiety disorder
SNRI	Selective serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
MAOI	Monoamine oxidase inhibitor
MAT	Multiple antidepressant therapy
PD	Panic disorder
PDD	Persistent depressive disorder
PPD	Postpartum depression
PPx	Prophylaxis
PTSD	Post-traumatic stress disorder
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCT	Randomized controlled trial
rTMS	Repetitive transcranial magnetic stimulation
TRD	Treatment-resistant depression
WFSBP	World Federation of Societies of Biological Psychiatry

1.0 INTRODUCTION

Mental health disorders affect approximately 17% of youth (6-17 years) in the United States (US) each year[1] and the prevalence of mental health disorders is on the rise.[2-4] As of 2020, approximately 9% of youth (3-17 years) endorsed anxiety problems and 4% reported depression in a nationally representative sample.[5] Many surveyed Utah adolescents reported symptoms of depression (35%) in 2021, a significant increase from 2019 (31%).[4] Educational performance,[6] familial relationships,[6] and social engagement are impaired during childhood among youth with mental health disorders,[7] and the presence of a mental health disorder during childhood is correlated with reduced life satisfaction and quality of life in adulthood.[7,8] Moreover, several mental health conditions such as depression are risk factors for self-harm.[9-12] In Utah, suicide is the most common cause of death among Utah adolescents,[4] and adolescent (15-19 years) suicide rates consistently exceeded national rates between 2012 and 2021.[13] In 2021, nearly 20% of surveyed Utah adolescents reported having suicidal ideations and 7% had attempted suicide in the past year.[4]

Despite the increased prevalence of mental health disorders, as little as 20% of youth receive treatment.[3] Moreover, those who do receive treatment may not be provided with an appropriate level of care.[14] The reasons for the apparent undertreatment of youth are likely complex and multi-factorial, including issues with access to non-pharmacologic psychosocial treatments (eg, psychotherapy)[15] that are a first line option for many mental, emotional, or behavioral conditions.[16] Antidepressants are an initial pharmacotherapy treatment option for several of the most common mental health disorders in youth.[16-18] Reports within the past 10 years indicate concerns for both under[19]- and over-utilization[20] of antidepressants in youth. Treatment of youth with antidepressants is sometimes controversial due to the US Food and Drug Administration's (FDA) black box warning for increased suicidality in people under 24 years old,[21,22] limited evidence contributing to off-label use,[21,23] possible differences in efficacy between adults and children,[22,24] and other toxicity concerns,[21,25] including theoretical adverse effects on brain development.[26,27] Evidence supporting use of antidepressants in very young children (ie, preschool age)[27,28] and for long-term use is particularly limited.[26]

Approximately 1.5-3% of youth are prescribed antidepressants,[29,30] and the prevalence of antidepressant use increases to as high as 7% among youth with severe psychological impairment.[29] In a 2014 sample of Medicaid youth from a mid-Atlantic state, differences were observed in the type of antidepressants used and prevalence of utilization by age. Selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) were the most prescribed antidepressants (2.14%).[30] Most antidepressant prescriptions were for youth aged 10-19 years; 0.87% of all youth ages 5-9 and 0.01% of all youth ages 0-4 were prescribed an antidepressant.[30]

Polypharmacy (using more than 1 medication for the same condition/symptom)[31] with multiple psychotropic medications is common among Medicaid youth,[30] and is a well-recognized concern due to the potentially increased risk of adverse reactions and uncertain benefit.[32,33] Studies report variable rates of antidepressant polypharmacy prescribing among youth ranging from about 1.6%[32] to 17%,[34] with the prevalence varying by country[34] and by US state.[32] Often, evidence for adult psychotropic polypharmacy is extrapolated to youth.[32,33]

To help guide appropriate use of antidepressants in Utah Medicaid youth (ages ≤ 17 years), the main objectives of this report are to (1) identify on-label (ie, FDA-approved uses) and potential off-label indications in youth, and the general place-in-therapy of antidepressants for target pediatric mental health conditions; (2) summarize indicated ages for use of antidepressants per compendia and clinical guidelines/guidance statements; and (3) describe supporting evidence or expert opinion on the concurrent use of multiple antidepressants in pediatric patients for target mental health conditions.

2.0 METHODS

This report addresses appropriate use of antidepressants in pediatrics with a focus on answering the following questions:

1. **Key Question 1**: What are on-label (FDA approved) uses and pharmacy compendia-recognized off-label uses for antidepressants in children or adolescents, and what is the place-in-therapy of antidepressants for target pediatric mental health conditions per guidelines or expert guidance?
2. **Key Question 2**: What is the youngest age recommended for use of antidepressants according to drug compendia, guidelines, or expert guidance on the treatment of target pediatric mental health disorders?
3. **Key Question 3**: What is the place in therapy for combined use of antidepressants (multiple antidepressant therapy [MAT]) for the treatment of target pediatric mental health disorders according to guidelines, expert guidance, or review articles?

We defined antidepressant as any unique active ingredient or combination of active ingredients classified as an "antidepressant" by the drug compendia Lexicomp (see **Appendix A**). For feasibility, **guideline/guidance for the key questions were limited to those addressing pharmacotherapy for pediatric unipolar depressive disorders, anxiety disorders, obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD).** These mental health conditions were selected as the focus for guideline information since they are known indications for antidepressants in adults.

2.1 Key Question 1 Methods

FDA-approved pediatric (age ≤ 17 years) uses for each antidepressant (defined per Appendix A) were extracted from the drug compendium Micromedex. The FDA-approved indications were extracted by unique drug product when the indication for an active ingredient varied by dosage form (eg, capsule versus tablet with same active ingredient), or formulation (eg, combination versus monotherapy product or unique salts). Pediatric off-label uses for antidepressants were extracted from the drug compendia Micromedex and Lexicomp. Ratings for recommendation class, level of evidence and strength of evidence were extracted from Micromedex for each off-label use; uses with a class III recommendation (ie, not recommended) or considered "not effective" were excluded. Potential off-label uses per Lexicomp were extracted regardless of the strength of evidence since this information was not available for any pediatric off-label antidepressant uses compiled by Lexicomp. Collected on-label* and off-label indications addressed both the target symptom/condition and supported pediatric

* Note that indications reported by Micromedex and Lexicomp often do not reflect the exact wording of FDA-approved uses, including not differentiating between when a drug is specifically approved for pediatric use and when pivotal trials included pediatric patients. For the exact nature of FDA approval for an antidepressant, consult the package insert.

age(s) for use, as provided by compendia. Off-label uses are reported using the compendia's terminology.

To provide additional guidance about appropriate use of antidepressants in pediatric patients, we also collected information from Micromedex and/or Lexicomp about the usual dosage range for on-label and off-label uses, when available, and contraindications. When available, literature-supported maximum pediatric doses for each antidepressant, regardless of indication, were collected from 2 US best practice guidance statements (the 2022-2023 Florida best practice psychotherapeutic guideline[16] and 2019 Texas Health and Human Services psychotropic medication parameter[35]). Antidepressant pediatric maximum dose information for any indication was additionally extracted from Micromedex and/or Lexicomp if it exceeded the maximum listed by the Florida or Texas guidance, or when no maximal dose was provided by the expert guidance.

2.2 Key Question 2 and 3 Methods

2.2.1 Guidelines or Expert Guidance Literature Search and Screening

We searched for recent (2018-2023) English language clinical practice guidelines or expert guidance statements from well-recognized organizations addressing drug therapy for treatment of children or adolescents with a unipolar depressive disorder, anxiety disorder, OCD, and/or PTSD. Two bibliographic databases (Ovid-Medline and Epistemonikos) were searched for guidelines or guidance statements, using search terms for antidepressants, target mental health conditions or symptoms, pediatrics, and guidelines or clinical consensus statements. Ovid-Medline search results were filtered for guidelines, clinical consensus, or expert guidance using a slightly modified version of a validated broad filter for guidelines from CADTH.[36] Refer to **Appendix B** for search details.

Databases searches for guidelines were supplemented by searches of the following websites on September 22, 2023:

- American Association of Psychiatric Pharmacists list of treatment guidelines for anxiety disorders and depression: https://aapp.org/guideline/external
- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/guidance/published?ngt=NICE%20guidelines
- American Academy of Child and Adolescent Psychiatry (AACAP) guidelines and practice parameters: https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx
- British Association for Psychopharmacology (BAP): https://www.bap.org.uk/docsbycategory.php?docCatID=2&page=1
- The Royal Australian & New Zealand College of Psychiatrists (RANZCP): https://www.ranzcp.org/clinical-guidelines-publications/clinical-guidelines-publications-library?publicationtype=clinicalguideline
- Canadian Network for Mood and Anxiety Treatments: https://www.canmat.org/resources/#health-professionals
- Scottish Intercollegiate Guideline Network (SIGN): https://www.sign.ac.uk/our-guidelines/

- American Psychiatric Association: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines
- American Psychological Association (APA): https://www.apa.org/about/policy/approved-guidelines
- Florida Center for Behavioral Health Improvements and Solutions (Child Guidelines): https://floridabhcenter.org/guidelines-child-list/
- US Department of Veterans Affairs (VA)/Department of Defense (DoD): https://www.healthquality.va.gov/
- International Society for Traumatic Stress Studies: https://istss.org/clinical-resources/treating-trauma/international-practice-guidelines-for-post-trauma
- Texas Department of Family and Protective Services Psychotropic Medications: https://www.dfps.texas.gov/Child_Protection/Medical_Services/Psychotropic_Medications.asp
- World Federation of Societies of Biological Psychiatry (WFSBP): https://wfsbp.org/educational-activities/treatment-cuidelines-and-consensus-paper/

The most recent version of a particular guideline from an organization addressing antidepressant treatment of pediatric patients with a targeted mental health condition (ie, depressive disorder, anxiety disorder, OCD, PTSD) was selected for inclusion. In addition to guidelines, we also considered expert consensus from major organizations (eg, established psychopharmacology or mental health treatment groups) that addressed pediatric pharmacotherapy for the target mental health conditions. Guidelines/guidance statements screened in full text and excluded are listed in **Appendix C.**

Information pertaining to key questions 1, 2 and 3 were extracted from included guidelines or expert opinion guidance statements. Additionally, on occasion we also extracted information from US guidelines/guidance statements published before 2018 to address areas minimally discussed by included guidelines/guidance statements, or for when no recent US guidelines from major organizations had been published. One notable older included US guidance is from Gleason et al (2007), which provides expert algorithms on the treatment of mental health disorders in preschool age children.[27]

2.2.2 Supplemental Multiple Antidepressant Therapy (MAT) Search and Screening

To supplement information from recent guidelines or expert guidance on MAT for the target pediatric mental health conditions, we performed a supplemental search for review or expert opinion articles. Two bibliographic databases (Ovid-Medline and Epistemonikos) were searched from inception to October 18th, 2023, using search terms for antidepressants, combination therapy (eg, combination or augment) and/or treatment resistance, and pediatrics. Search results were filtered for review or expert opinion articles using an independently derived filter in Ovid-Medline and built-in filters for systematic reviews, broad syntheses, or structured summaries in Epistemonikos. The adapted filter in Ovid-Medline combined a modified version of the McMaster University systematic review filter[37] with parts of validated guideline filters for consensus or treatment pathways from CADTH.[36] Refer to **Appendix B** for details of the literature searches.

Titles and abstracts from the supplemental search were screened by a single author for information about multiple antidepressant therapy or treatment resistance for any condition in pediatric patients.

Full text screening of the subset of articles identified by title and abstract screening was performed independently by two authors without duplication.

Relevant findings addressing antidepressant polypharmacy outside of the setting of cross-titration when switching between antidepressant monotherapy were extracted from review articles. When review articles lacked details about which antidepressants were combined, primary articles cited by the review article were reviewed for additional information.

3.0 ANTIDEPRESSANTS OVERVIEW

There are 36 unique active ingredients classified as having antidepressant activity by Lexicomp (see **Appendix A Table A1**) that are usually classified according to their pharmacologic action (eg, SSRIs), or chemical structure (eg, tricyclic antidepressants [TCAs]). Antidepressants possess variable pharmacology, with heterogeneity among antidepressants of the same class. Notably, most antidepressants boost serotonergic neurotransmission, including the TCAs, which are serotonin and norepinephrine reuptake inhibitors.[38] Newer antidepressant classes with comparatively less serotonergic activity, if any, include the N-methyl-D-aspartate (NDMA) receptor antagonists which boost glutamatergic neurotransmission (eg, esketamine),[39,40] and neurosteroids, brexanolone and zuranolone, that modulate GABA (gamma-aminobutryric acid) neurotransmission.[41,42] Bupropion, a dopamine and norepinephrine reuptake inhibitor (DNRI), also primarily boosts non-serotonergic neurotransmission.[43] Older classes of antidepressants, including TCAs and monoamine oxidase inhibitors (MAOIs), are infrequently used to treat mental health conditions today due to having a worse safety profile compared to newer antidepressants (eg, SSRIs).[35,44] SSRIs and less commonly, SNRIs, are the antidepressant drug classes usually recommended as first line pharmacotherapy for depressive disorders, anxiety disorders, OCD, and some other mental health conditions in children and adolescents.[16]

Many antidepressants are available in multiple formulations, and some antidepressants such as bupropion and imipramine, are available as different salts (eg, bupropion hydrobromide versus hydrochloride).[45-48] Combination products of an antidepressant with an anxiolytic and/or antipsychotic are available for amitriptyline and fluoxetine.[49-51] Additionally, dextromethorphan/bupropion is available as a combination product of 2 antidepressants.[52] Refer to **Appendix A Table A2** for available antidepressant formulations. FDA approval and evidence for use in pediatric patients sometimes varies by antidepressant formulation. For simplicity, throughout this report, we primarily discuss antidepressants by active ingredient (eg, bupropion instead of bupropion hydrochloride).

4.0 ANTIDEPRESSANT PEDIATRIC OFF-LABEL AND FDA-APPROVED INDICATIONS PER COMPENDIA (KEY QUESTION 1)

Table 1 below summarizes FDA-approved pediatric indications, and possible off-label pediatric uses according to the drug compendium, Micromedex or Lexicomp, for each of the reviewed antidepressants. FDA-approved indications are shown in orange and compendia-recognized off-label uses are shown in dark gray. Off-label uses are included in the table when listed by at least 1 compendium (ie, Micromedex or Lexicomp). Included off-label indications from Micromedex are those recommended in all, most, or some cases. Off-label uses from Lexicomp were included regardless of recommendation strength (as Lexicomp did not grade the evidence), unless the indication overlapped with an indication that

Micromedex evaluated as not recommended. The youngest recognized age to start a particular antidepressant per indication is also shown in Table 1; this information is per FDA approval, or per clinical evidence, as mentioned by compendia.

More details about antidepressant indications, dosing, and contraindications are provided in **Appendix D** and **Appendix E.** See **Table D1** for the FDA-approved pediatric indications and usual dosage range by antidepressant formulation, literature supported (per recent US guidances[16,35]) or compendia-recognized maximum dosages, and contraindications. Refer to **Table E1** for pediatric off-label uses and dosing information per Micromedex and Lexicomp for each of the reviewed antidepressants. Micromedex ratings for evidence categories (eg, evidence favors efficacy), strength of evidence (types of evidence to support use), and overall recommendation class are also provided in Table E1. Most pediatric off-label uses recommended by Micromedex are supported by *level B* evidence (ie, non-randomized studies, low-quality RCTs, or meta-analyses with conflicting results) and some are *level C* (expert opinion). Only 3 possible off-label pediatric uses per Micromedex received *level A* evidence ratings (eg, good-quality RCTs): sertraline for generalized anxiety disorder (GAD), bupropion for attention-deficit/hyperactivity disorder (ADHD), and ketamine for moderate to severe acute pain.[45,53,54]

4.1 Indications Overview

Overall, there are few FDA-approved pediatric indications for antidepressants (see Table 1).

- Mental health disorders[†] with FDA approval for pediatric treatment with at least 1 antidepressant include:
  - Depressive disorders including major depressive disorder (SSRIs, escitalopram, fluoxetine)[51,55]; depression with or without other comorbidities (most TCAs[56-60]; MAOI, isocarboxazid)[61]; bipolar depression (fluoxetine/olanzapine)[51]; and postpartum depression (brexanolone)[62]
  - Anxiety disorders including GAD (SSRI, escitalopram[55]; SNRI, duloxetine[63]); anxiety (TCA, doxepin)[57]; and anxiety associated with alcoholism (TCA, doxepin)[57]
  - OCD (SSRIs, fluoxetine, fluvoxamine, and sertraline[51,53,64]; TCA, clomipramine)[65]
- Other disorders with FDA approval for pediatric treatment with at least 1 antidepressant include:
  - Fibromyalgia (SNRI, duloxetine)[63]; nocturnal enuresis (TCA, imipramine)[48]; and general anesthesia (NMDA antagonist, ketamine)[54]

In comparison to the pediatric on-label uses, there exist a greater number of potential off-label pediatric indications recognized by at least 1 drug compendium for antidepressants (see Table 1).

- Potential off-label pediatric uses for at least 1 antidepressant per Micromedex and/or Lexicomp include:
  - Mental health conditions:
    - Major depressive disorder (SSRIs, fluvoxamine,[66] and sertraline[53,67]; SNRI, venlafaxine[68,69]; and MAOI, tranylcypromine)[70]; depression (SSRI, citalopram[71]; TCAs, clomipramine,[65] desipramine,[72] imipramine,[73] and doxepin or nortriptyline [at a younger age than FDA approval])[58,74,75]; and MAOI, transdermal selegiline)[76]; refractory depression (DNRI, bupropion)[43]; and atypical or non-endogenous depression (MAOI, phenelzine)[77]

[†] In Table 1, mental health conditions include any disorder recognized by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text-Revision (DSM-5-TR)

- Anxiety disorders including GAD (SSRIs, citalopram, fluoxetine, sertraline[51,53,71]; SNRI, venlafaxine[68,69]); anxiety (TCA, doxepin)[74]; panic disorder (SSRIs, citalopram, fluoxetine, paroxetine[78-80]; SNRI, venlafaxine)[69]; social anxiety disorder (SSRIs, citalopram, escitalopram, fluoxetine, paroxetine[51,71,80-82]; SNRI, venlafaxine)[68,69]; separation anxiety disorder (SSRIs, citalopram, fluoxetine[51,71,79]; SNRI, venlafaxine),[69] and selective mutism (SSRI, fluoxetine)[79]
- Bulimia nervosa, or anorexia nervosa (SSRI, fluoxetine)[79]
- Insomnia/sleep disturbances (serotonin reuptake inhibitor/antagonist, trazodone)[83]
- ADHD (DNRI, bupropion[43,45]; and several TCAs)[58,72,73,75,84]

- Other conditions:
  - Migraine or headache prophylaxis or treatment (TCA, amitriptyline[56,85]; and serotonin reuptake inhibitor/antagonist, trazodone)[83]
  - Cyclic vomiting syndrome (TCA, amitriptyline)[85]
  - Irritable bowel syndrome (TCA, amitriptyline)[56]
  - Urinary incontinence (TCA, imipramine)[48]
  - Chronic pain (TCA, amitriptyline)[85]; neuropathic pain (TCA, nortriptyline)[75]; or acute pain (NMDA antagonist, ketamine)[39,54]
  - Smoking cessation (DNRI, bupropion)[43]
  - Nocturnal enuresis (TCA, nortriptyline)[58]
  - Rapid intubation (NMDA antagonist, ketamine)[54]

Consistent with clinical practice guidelines that frequently consider SSRIs as a first line option for several mental health disorders in youth when pharmacotherapy is indicated,[16-18,86] SSRIs may be used for the most mental health indications (on-label or off-label) of any drug class. All SSRIs are recognized by a drug compendium for at least 1 pediatric mental health indication except vortioxetine and vilazodone.[51,53,55,64,66,67,71,78-82,87-90] Fluoxetine showed the most versatility, with indications for the treatment of MDD and OCD (FDA-approved), anxiety disorders (off-label), and eating disorders (off-label).[51,79] Fluoxetine is also the only antidepressant reported as possibly useful for selective mutism (off-label).[79] Citalopram also has indications for the treatment of depressive disorders, a wide range of anxiety disorders and OCD, without carrying FDA approval for any pediatric condition.[71,78] Escitalopram, paroxetine and sertraline also may be used for at least 3 different indications; paroxetine is not FDA approved for any pediatric condition unlike escitalopram and sertraline.[53,55,67,80-82]

Of the 5 SNRIs, only duloxetine and venlafaxine have potential indications for pediatric use. Duloxetine is the only SNRI with an FDA-approved use, for the treatment of GAD and fibromyalgia.[63] Venlafaxine has the most varied indications, having been used off-label for the treatment of depressive and anxiety disorders, as well as ADHD.[68,69]

Among other drug classes, TCAs, except amoxapine and amitriptyline combinations, have at least 1 pediatric mental health indication (on-label or off-label).[48,56-60,65,72-75,84,85,91-93] All four MAOIs, including transdermal but not oral selegiline, show only depressive disorders as a potential pediatric on-label (isocarboxazid only) or off-label use. [61,70,77,94] And of antidepressants with varied other drug classes, only bupropion, brexanolone, ketamine, and trazodone show potential pediatric uses, primarily off-label.[43,45,54,62,83] Notably, brexanolone is the only antidepressant with an indication for postpartum depression (on-label for ages ≥ 15 years).[62]

Table 1. Overview of FDA-Approved Pediatric Indications and Recommended Off-Label Pediatric Uses, per Drug Compendium (Micromedex or Lexicomp)

Antidepressant	**FDA-Approved Pediatric Indication** or Compendia-Recognized Off-Label (OL) Pediatric Uses (approved/recommended ages, if available in compendia)[a]									
	Depressive disorders (Specified below)	**Anxiety Disorders**				**Other Mental Health Disorder**				**Non-mental health indications** (Specified below)
		GAD	**PD**	**SAD**	**Other anxiety disorders**	**OCD**	**ADHD**	**Sleep Disorders**	**Eating disorders**	
Selective serotonin reuptake inhibitors (SSRIs)										
Citalopram[71,78]	OL[b]—Depression (Age 7+)	OL[b] (Age 7+)	OL[c] (Age 7+)	OL[b] (Age 7+)	OL[b]—Separation Anx (Age 7+)	OL (Age 6+)				
Escitalopram[55,81]	**X—MDD (Age 12+)**	**X (Age 7+)**		OL[b] (Age 7+)						
Fluoxetine[51,79]	**X—MDD (Age 8+)**	OL[c] (Age 6+)	OL[c] (Age 6+)	OL[c] (Age 11+)	OL[c]—Separation Anx (Age 6+) OL[b]—Selective Mutism (Age 5+)	**X (Age 7+)**			OL[c]—Bulimia N. (Age 12+) OL[b]—Anorexia N. (Adolescents)	
Fluoxetine with olanzapine[51,79]	**X—BPD (Age 10+)**									
Fluvoxamine[64,66]	OL—MDD (Age 12+)					**X (Age 8+)**				
Paroxetine[80,82,95]			OL[c] (Age NR)	OL (Age 8+)		OL (Age 7+)				
Sertraline[53,67]	OL[c]—MDD (Age 6+)	OL (Age 7+)				**X (Age 6+)**				
Vortioxetine[89,90]	No approved or compendia-recognized pediatric indications									
Vilazodone[87,88]	No approved or compendia-recognized pediatric indications									
Serotonin-norepinephrine reuptake inhibitors (SNRIs)										
Desvenlafaxine[96,97]	No approved or compendia-recognized pediatric indications									
Duloxetine[63,98]		**X (Age 7+)**								**X–Fibromyalgia (Age 13+)**
Levomilnacipran[99,100]	No approved or compendia-recognized pediatric indications									
Milnacipran[101,102]	No approved or compendia-recognized pediatric indications									
Venlafaxine[68,69]	OL[c]—MDD (Age 12+)	OL (Age 6+)	OL[b] (Age 6+)	OL (Age 8+)	OL[b]—Separation Anx (Age 6+)		OL (Age 6+)			
Tricyclic antidepressants (TCAs)										
Amitriptyline[56,85]	**X[c]—Depression (Age 12+)**									OL[b]—CVS (Age 5+)

Shading: *Cells highlighted in orange are FDA approved for the indication listed. Cells highlighted in dark gray are listed in compendia (Lexicomp and/or Micromedex) as possible off-label uses, and light gray indicates the lack of FDA approval or compendia-recognized use. Unless otherwise indicated (with b/c superscript), Micromedex rated evidence for the off-label indication is as "evidence favors efficacy" in Micromedex.*

[a] *Indications may not match the FDA-approved indication exactly; refer to individual prescribing information for details. Indications for an antidepressant are listed when at least 1 antidepressant formulation with that active ingredient has an approved/recognized use. However, indications sometimes vary by antidepressant formulation. Please see Appendixes D and E for more details about indications for each formulation.* ***Note that in some cases guideline-recognized uses differ from compendia-recognized uses; please see sections 6.2 to 6.5 of this report for guideline-recognized antidepressant uses for target conditions (ie, depressive disorders, anxiety disorders, OCD, and PTSD).***

[b] *Off-label indication is listed in Lexicomp, but not listed in Micromedex.*

[c] *Off-label use in Micromedex is listed as "evidence is inconclusive" for efficacy.*

Abbreviations: ADHD, attention deficit hyperactivity disorder; Anx, anxiety; BPD, bipolar disorder I depression; CVS, cyclic vomiting syndrome; GAD, generalized anxiety disorder; IBS, irritable bowel syndrome; MDD, major depressive disorder; Mo, months; N., nervosa; NR, not reported or insufficient information to discern from compendia; OCD, obsessive compulsive disorder; OL, off-label; PD, panic disorder; PPD, post-partum depression; PPx, prophylaxis; SAD, social anxiety disorder/social phobia, Tx, treatment

Table 1. Overview of FDA-Approved Pediatric Indications and Recommended Off-Label Pediatric Uses, per Drug Compendium (Micromedex or Lexicomp)

Antidepressant	**FDA-Approved Pediatric Indication** or Compendia-Recognized Off-Label (OL) Pediatric Uses (approved/recommended ages, if available in compendia)[a]								
	Depressive disorders (Specified below)	**Anxiety Disorders**				**Other Mental Health Disorder**				**Non-mental health indications** (Specified below)
		GAD	**PD**	**SAD**	**Other anxiety disorders**	**OCD**	**ADHD**	**Sleep Disorders**	**Eating disorders**	
										OL[b]—Migraine PPx (Age 8+)
	OL[c]—Depression (Age 9-12)									OL[c]—IBS (Adolescents) OL[c]- Headache Tx and Ppx (Age NR) OL[b] —chronic pain (Age NR)
Amitriptyline-chlordiazepoxide[50,103]	No approved or compendia-recognized pediatric indications									
Amitriptyline-phenelzine[49,104]	No approved or compendia-recognized pediatric indications									
Amoxapine[105,106]	No approved or compendia-recognized pediatric indications									
Clomipramine[65,91]	OL—Depression (Age 14+)					**X (Age 10+)**				
Desipramine[72,84]	OL[b]—Depression (Age 6+)						OL (Age 7+)			
Doxepin[57,74]	**X—Depression (Age 12+)** **X—Depression associated with alcoholism (Age 12+)** **X—Psychotic depressive disorders with associated anxiety (Age 12+)** OL[b]—Depression (Age 7-11)				**X—Anxiety or Anxiety associated with alcoholism (Age 12+)** OL[b] – Anxiety (Age 7-11)					
Imipramine[47,48,73]	OL[b]—Depression (Age 8+)						OL[b] (Age 6+)			**X—Nocturnal enuresis (Age 6+)** OL[c]—Urinary incontinence (Age NR)
Nortriptyline[58,75]	**X—Depression (Adolescents)** OL[c]—Depression (Age 5+)						OL (NR)			OL—Nocturnal enuresis (Age 6+) OL[b]—Neuropathic pain (Age NR)

Shading: *Cells highlighted in orange are FDA approved for the indication listed. Cells highlighted in dark gray are listed in compendia (Lexicomp and/or Micromedex) as possible off-label uses, and light gray indicates the lack of FDA approval or compendia-recognized use. Unless otherwise indicated (with b/c superscript), Micromedex rated evidence for the off-label indication is as "evidence favors efficacy" in Micromedex.*

[a] *Indications may not match the FDA-approved indication exactly; refer to individual prescribing information for details. Indications for an antidepressant are listed when at least 1 antidepressant formulation with that active ingredient has an approved/recognized use. However, indications sometimes vary by antidepressant formulation. Please see Appendixes D and E for more details about indications for each formulation.* ***Note that in some cases guideline-recognized uses differ from compendia-recognized uses; please see sections 6.2 to 6.5 of this report for guideline-recognized antidepressant uses for target conditions (ie, depressive disorders, anxiety disorders, OCD, and PTSD).***

[b] *Off-label indication is listed in Lexicomp, but not listed in Micromedex.*

[c] *Off-label use in Micromedex is listed as "evidence is inconclusive" for efficacy.*

Abbreviations: ADHD, attention deficit hyperactivity disorder; Anx, anxiety; BPD, bipolar disorder I depression; CVS, cyclic vomiting syndrome; GAD, generalized anxiety disorder; IBS, irritable bowel syndrome; MDD, major depressive disorder; Mo, months; N., nervosa; NR, not reported or insufficient information to discern from compendia; OCD, obsessive compulsive disorder; OL, off-label; PD, panic disorder; PPD, post-partum depression; PPx, prophylaxis; SAD, social anxiety disorder/social phobia, Tx, treatment

Table 1. Overview of FDA-Approved Pediatric Indications and Recommended Off-Label Pediatric Uses, per Drug Compendium (Micromedex or Lexicomp)

Antidepressant	**FDA-Approved Pediatric Indication** or Compendia-Recognized Off-Label (OL) Pediatric Uses (approved/recommended ages, if available in compendia)[a]								
	Depressive disorders (Specified below)	**Anxiety Disorders**				**Other Mental Health Disorder**				**Non-mental health indications** (Specified below)
		GAD	**PD**	**SAD**	**Other anxiety disorders**	**OCD**	**ADHD**	**Sleep Disorders**	**Eating disorders**	
Protriptyline[59,92]	**X—Depression (Adolescents)**									
Trimipramine[60,93]	**X—Depression (Adolescents)**									
Monoamine oxidase inhibitors (MAOIs)										
Isocarboxazid[61,107]	**X—Depression (Age 16+)**									
Phenelzine[77,108]	OL—Atypical or non-endogenous depression (Age NR)									
Selegiline[76,94,109]	OL[b]—Depression (Age 17+)									
Tranylcypromine[70,110]	OL—MDD, second-line therapy (Age NR)									
Antidepressants with other drug classes										
Bupropion[43,45,46]	OL[b]-Refractory depression (Age 8+)						OL (Age 6+)			OL[b]—Smoking cessation (Age 14+)
Bupropion-Dextromethorphan[52,111]	No approved or compendia-recognized pediatric indications									
Brexanolone[41,62]	**X—PPD (Age 15+)**									
Esketamine[40,112]	No approved or compendia-recognized pediatric indications									
Gepirone[113-115]	No approved or compendia-recognized pediatric indications									
Ketamine[39,54]										**X—General anesthesia, induction of anesthesia, procedural sedation (Age 16+)** OL—General anesthesia, induction of anesthesia, procedural sedation (Age 5 days+) OL—Acute pain (Age 3+)

Shading: *Cells highlighted in orange are FDA approved for the indication listed. Cells highlighted in dark gray are listed in compendia (Lexicomp and/or Micromedex) as possible off-label uses, and light gray indicates the lack of FDA approval or compendia-recognized use. Unless otherwise indicated (with b/c superscript), Micromedex rated evidence for the off-label indication is as "evidence favors efficacy" in Micromedex.*

[a] *Indications may not match the FDA-approved indication exactly; refer to individual prescribing information for details. Indications for an antidepressant are listed when at least 1 antidepressant formulation with that active ingredient has an approved/recognized use. However, indications sometimes vary by antidepressant formulation. Please see Appendixes D and E for more details about indications for each formulation.* ***Note that in some cases guideline-recognized uses differ from compendia-recognized uses; please see sections 6.2 to 6.5 of this report for guideline-recognized antidepressant uses for target conditions (ie, depressive disorders, anxiety disorders, OCD, and PTSD).***

[b] *Off-label indication is listed in Lexicomp, but not listed in Micromedex.*

[c] *Off-label use in Micromedex is listed as "evidence is inconclusive" for efficacy.*

Abbreviations: ADHD, attention deficit hyperactivity disorder; Anx, anxiety; BPD, bipolar disorder I depression; CVS, cyclic vomiting syndrome; GAD, generalized anxiety disorder; IBS, irritable bowel syndrome; MDD, major depressive disorder; Mo, months; N., nervosa; NR, not reported or insufficient information to discern from compendia; OCD, obsessive compulsive disorder; OL, off-label; PD, panic disorder; PPD, post-partum depression; PPx, prophylaxis; SAD, social anxiety disorder/social phobia, Tx, treatment

Table 1. Overview of FDA-Approved Pediatric Indications and Recommended Off-Label Pediatric Uses, per Drug Compendium (Micromedex or Lexicomp)

Antidepressant	**FDA-Approved Pediatric Indication** or Compendia-Recognized Off-Label (OL) Pediatric Uses (approved/recommended ages, if available in compendia)[a]								
	Depressive disorders (Specified below)	**Anxiety Disorders**				**Other Mental Health Disorder**				**Non-mental health indications** (Specified below)
		GAD	**PD**	**SAD**	**Other anxiety disorders**	**OCD**	**ADHD**	**Sleep Disorders**	**Eating disorders**	
										OL[c]—rapid intubation (Age 0+)
Mirtazapine[116,117]	No approved or compendia-recognized pediatric indications									
Nefazodone[118,119]	No approved or compendia-recognized pediatric indications									
Trazodone[83,120]								OL[b]—Insomnia, sleep disturbances (Age 18 mo+)		OL[b]—Migraine PPx, (Age 7+)
Zuranolone[42,121]	No approved or compendia-recognized pediatric indications									

Shading: *Cells highlighted in orange are FDA approved for the indication listed. Cells highlighted in dark gray are listed in compendia (Lexicomp and/or Micromedex) as possible off-label uses, and light gray indicates the lack of FDA approval or compendia-recognized use. Unless otherwise indicated (with b/c superscript), Micromedex rated evidence for the off-label indication is as "evidence favors efficacy" in Micromedex.*

[a] *Indications may not match the FDA-approved indication exactly; refer to individual prescribing information for details. Indications for an antidepressant are listed when at least 1 antidepressant formulation with that active ingredient has an approved/recognized use. However, indications sometimes vary by antidepressant formulation. Please see Appendixes D and E for more details about indications for each formulation.* ***Note that in some cases guideline-recognized uses differ from compendia-recognized uses; please see sections 6.2 to 6.5 of this report for guideline-recognized antidepressant uses for target conditions (ie, depressive disorders, anxiety disorders, OCD, and PTSD).***

[b] *Off-label indication is listed in Lexicomp, but not listed in Micromedex.*

[c] *Off-label use in Micromedex is listed as "evidence is inconclusive" for efficacy.*

Abbreviations: ADHD, attention deficit hyperactivity disorder; Anx, anxiety; BPD, bipolar disorder I depression; CVS, cyclic vomiting syndrome; GAD, generalized anxiety disorder; IBS, irritable bowel syndrome; MDD, major depressive disorder; Mo, months; N., nervosa; NR, not reported or insufficient information to discern from compendia; OCD, obsessive compulsive disorder; OL, off-label; PD, panic disorder; PPD, post-partum depression; PPx, prophylaxis; SAD, social anxiety disorder/social phobia, Tx, treatment

5.0 INDICATED AGE FOR TREATMENT (KEY QUESTION 2)

The compendia-suggested age range for use varies by antidepressant and indication (see Table 1). Information about age (eg, inferred from ages included in clinical studies, or from suggested dosing) was not available in compendia for every indication.

Most indications have antidepressants that can be used from the youngest ages of 6 to 8 years old, with a few outliers starting earlier at the age of 5, and a few indications (eating disorders and some non-mental health indications) that are for adolescents only. The youngest recognized age for receiving an antidepressant for any indication is infancy, specifically for short-term use of ketamine for anesthesia or rapid intubation (off-label).[39,54] Trazodone has been used (off-label) to help with insomnia and sleep disturbances in children as young as 18 months old.[83] Six years old is the youngest indicated age for any FDA-approved use, for treatment of OCD with sertraline and treatment of nocturnal enuresis with imipramine.[48,53]

By drug class, SSRIs and SNRIs tend to the have the youngest age range for general use; fluoxetine may be used (off-label) at the youngest age (≥ 5 years for selective mutism).[79] TCAs are primarily FDA approved for ages ≥ 12 years but may be used off-label for children as young as 5 years old.[48,56-60,65,84] Use of MAOIs appears to be generally reserved for older adolescents.[61,70,76,77] Bupropion has been used off label for ADHD in children age 6 years or older.[43,45]

5.1 Recommended Antidepressant Dose for Pediatrics

Limited[‡] pediatric antidepressant dosing information for FDA approved and off-label (when available) uses are summarized in **Appendix D** and **Appendix E**. Dosing strategies vary by antidepressant, age, dosage form, and indication. In some cases, the literature-supported maximum dose for any pediatric indication exceeds the FDA-approved pediatric dose, for example, for escitalopram[35,81] and fluoxetine.[16,51]

This information is intended to provide an overview of the typical dosage range and maximum dose used in children or adolescents. Keep in mind that dosing strategies recorded in the Appendices D and E, particularly those for off-label uses, could reflect doses used in a single study that may be inconsistent with current practices. For example, while evidence may support using doses up to 70 mg daily of citalopram in adolescents,[78] it is usually advised to not exceed 40 mg daily due to the dose-related risk of QT prolongation.[71]

6.0 GUIDELINES OR GUIDANCE ON ANTIDEPRESSANT PLACE-IN-THERAPY, INDICATED AGES, AND USE OF MULTIPLE ANTIDEPRESSANTS IN YOUTH

The following sections address key objectives 1, 2 and 3, regarding the place in therapy of antidepressants, guideline-recommended ages for use of antidepressants in youth, and guideline or

[‡] Dosing information lacks starting doses and guidance about adult doses (typically pediatric doses should not exceed the adult dose). Please consult the respective prescribing information for dosing details.

expert opinion on the use of multiple antidepressants, primarily for the target conditions of depressive disorders, anxiety disorders, OCD, and PTSD. Notably**, there are a few guideline-recognized antidepressant uses for target conditions that are not recognized by compendia (Lexicomp or Micromedex).** For example, according to the AACAP, all SSRIs are an option to treat most anxiety disorders,[17] in contrast with potential uses per compendia, which report no potential anxiety indications for several SSRIs (eg, fluvoxamine) and fewer anxiety indications for other SSRIs (eg, escitalopram).[53,55,64,66,67,80-82]

Section 6.1 addresses general recommendations, including minimum age for antidepressant use and/or antidepressant polypharmacy, from recent US guidance (from Texas and Florida) or expert opinion. Sections after 6.1 are organized by target condition and include an overview of recent guideline recommendations for the target disorders, highlighting guideline or guidance information on the antidepressants place-in-therapy, the recommended age for using antidepressants, and multiple antidepressant therapy (MAT). Information about MAT from reviews is also addressed by condition.

6.1 General Antidepressant or Psychotropic Recommendations

6.1.1 Texas Guideline on Use of Psychotropic Agents in Youth

The Texas Department of Health and Human Services (DHHS) published the 2019 (6th edition) "Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health"[§] to guide best practices for using psychotropic medications to treat youth receiving care from the Texas behavioral health systems.[35]

Select informal recommendations (all recommendations are non-graded) by Texas DHHS guidance are as follows[35]:

- "…it is important that a comprehensive evaluation be performed before beginning treatment for a mental or behavioral disorder. Except for in the case of an emergency, a child should receive a thorough health history, psychosocial history, mental status exam, and physical exam before prescribing a psychotropic medication" (page 5). When needed, medications should target a documented DSM-5 diagnosis (preferred), or at a minimum, target symptoms in the absence of sufficient evidence for a diagnosis.
- Non-pharmacologic treatments (eg, psychotherapy or environmental changes) are important treatment options for mental health conditions in general, particularly for youth with mild presentations.
- Although many medications lack FDA approval for use in children, "Studies and expert clinical experience often support the use of a medication for an 'off-label' use" (page 7). Notably**, off-label use of medications "…is particularly relevant in child psychiatry as there is a dearth of FDA-registration trials in youth"** (page 7).
- When switching between antidepressants used at high doses, exercise caution to reduce serotonin syndrome risk. Overlap while switching between psychotropic medications (cross-tapering) may be considered to switch between antidepressants from different drug classes, whereas a "direct

[§] Developed by the Parameters Workgroup of the Psychiatric Executive Formulary Committee with input provided by several pharmacy or medical schools in Texas. Versions of this parameters have been published since 2004.

switch" (start of the new medication the day after the last dose of the old medication) can be considered for changes between SSRIs. Cross-tapering usually occurs within 4 weeks.

- **Regarding combined use psychotropic medications to treat the same condition:**
  - In most cases, medications targeting a particular condition or symptom should be started one at a time. "When polypharmacy regimens are needed, addition of medications should occur in a systematic orderly process, accompanied by on-going monitoring, evaluation, and documentation" (page 8).
  - Concomitant use of ≥ 2 antidepressants is a suggested criterion for additional review of the child's clinical status. Use of 2 or more antidepressants concurrently is not automatically inappropriate, but it should trigger a careful review of necessity for the patient's condition.
- **Regarding a minimum age for use of antidepressants in youth:**
  - Use of an antidepressant for children under 4 years old is a suggested criterion for additional review of the child's clinical status.
- Specific medication recommendations:
  - For select antidepressants addressed by the Texas DHHS guidance, a literature-based maximal dosage is provided. Antidepressant doses exceeding the literature-based maximal dosage is a criterion for additional review of the child's clinical status. In some circumstances, providers may consider it to be necessary to exceed the literature-recommended maximal dose; in these cases, the provider should carefully document a rationale and monitor the patient's treatment response. Providers should consider alternate options or a decrease in dosage for lack of improvement at the higher dosage within a reasonable period (eg, 2-4 weeks).
  - The Texas guidance does not address all antidepressants; *often, agents not addressed by the parameter are those with insufficient evidence for use in youth*.
    - Antidepressants not included/recommended (rationale/concern, if provided) for youth:
      - TCAs–all unless otherwise noted, venlafaxine (possible harm), levomilnacipran (insufficient evidence), vortioxetine (insufficient evidence), MAOIs–except transdermal selegiline (increased adverse event [AE] and safety issues)
    - The following antidepressants are included/recommended by the Texas practice parameter:
      - Bupropion[**], citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, vilazodone, duloxetine, desvenlafaxine, clomipramine, mirtazapine, selegiline (as Emsam, the transdermal preparation), and trazodone[††]
        - Note that Lexicomp and/or Micromedex do not recognize potential uses for desvenlafaxine or vilazodone,[87,88,96,97] unlike the Texas guidance. Texas provided dosing information for vilazodone (in adolescents 12-17) and desvenlafaxine (in youth 7-17 years) based on published trials for major depressive disorder (MDD),[35] which failed to demonstrate efficacy for those agents.[122-124]

[**] Bupropion is listed as an alternative option for ADHD by the Texas DHHS guidance
[††] Trazodone is considered a sedative/hypnotic option by the Texas DHHS guidance

6.1.2 Florida Best Practices for Using Psychotherapeutics in Youth

The Florida Center for Behavioral Health Improvements and University of South Florida published 2022-2023 expert consensus guidance for use of psychotropic agents in children and adolescents. Part of the guideline addresses general principles for prescribing medications to treat mental health conditions in children under 6 years, and children 6-17 years old. A few general principles from this guideline are noted below; refer to the guidance for details.

- For all youth, it is recommended that providers complete a comprehensive mental health assessment before prescribing any psychotherapeutic agents. This assessment should include ruling out other causes of the child or adolescent's behavioral problems, among other assessments. Evaluation of mental health symptoms with age-appropriate questionnaires is recommended.
- For children and adolescents, psychosocial treatments are usually recommended first, unless the severity of the child's illness warrants additional intervention. Medications should only be initiated after careful consideration of the risks versus benefits, in consultation with the youth and their guardian(s). Initiate treatment with monotherapy and continue treatment as monotherapy (except in rare cases). For children 6 years and younger, use the lowest effective dose. Psychosocial interventions should be continued during medication therapy.
- "Use of psychotherapeutic medication in children under the age of 24 months is not recommended unless there are rare and extenuating circumstances" (page 4).[16]

6.1.3 Expert Opinion (2013) on Combining Psychotropic Medications in Youth

In 2013, Jureidini and colleagues examined the prevalence, rationale, risks, and benefits of psychotropic polypharmacy (defined as ≥ 2 medications for the same condition) in youth. Generally, possible rationales for combining mediations include partial or ineffectiveness of monotherapy, temporary acute use (eg, for sedation in acute mania), the management of adverse effects of another medication, or for treating comorbidities. Nonetheless, combination therapy increases the risk of drug-drug interactions and adverse drug reactions, which may occur at higher rates in pediatric patients than adults. Juriedini et al searched for evidence comparing combination therapy to monotherapy in youth and did not find such evidence for antidepressants addressed by this report.[33] However, one 5-week RCT evaluated combination therapy with fluoxetine (20 mg daily) and atomoxetine, a selective norepinephrine reuptake inhibitor with pharmacologic activity overlapping with some antidepressants, among youth (7-17 years) with ADHD and depression or anxiety. Combination therapy exhibited an overall comparable tolerability with similar discontinuation rates, but a higher incidence of increased mean heart rate, blood pressure, and decreased appetite occurred with combination fluoxetine and atomoxetine therapy than atomoxetine monotherapy.[125]

Given the limited high-quality evidence for psychotropic polypharmacy in youth, Jureidini et al provided the following guidance to help clinicians evaluate initiating polypharmacy (page 388)[33]:

1. "Why is the combination being considered? If it is for sub-therapeutic response to a monotherapy, has the necessary review of the case and monotherapeutic optimization been conducted?"
2. "Is there a clinical and pathophysiological rational for the combination?"
3. "Is there scientific literature that addresses the combination being considered?"

4. "Are there known or likely drug-drug interactions?"

Once combination therapy is initiated, Jureidini et al advises that clinicians should specify the planned duration for the combination therapy trial and efficacy and safety monitoring.[33]

6.2 Unipolar Depressive Disorders

Depressive disorders are characterized by persistent feelings of sadness, hopelessness, and/or irritability that significantly impair daily activities. While "depression" often refers to MDD, depressive disorders also include persistent depressive disorder (previously called dysthymia), premenstrual dysphoric disorder, disruptive mood dysregulation disorder (DMDD), and others. Persistent depressive disorder (PDD) is lasting depressive symptoms (duration ≥ 1 year in children) that are present most days of the week.[10] Duration between MDD episodes and symptom severity varies[10]; rarely, psychotic symptoms occur in severe cases.[18] Suicidal thoughts or ideas (ie, suicidal ideation) and attempts are common among people with MDD.[10,18] Adolescents are more likely than children to exhibit suicidality.[18] MDD recurs in at least 70% of cases.[18]

Depression is one of the most common mental health diagnoses in children and adolescents. In a 2016 nationally representative survey of US households, 3% of children (ages 3-17 years) had a current diagnosis of depression.[126] Depressive disorders may occur at any age, including among preschool age children, but adolescents experience depressive disorders at higher rates than prepubescent children.[18] Co-occurring mental health diagnoses are common, affecting up to 90% of youth with depression.[18]

In total, we reviewed 11 recent pediatric depression treatment guidelines or guidance statements for information about the key questions of this report: 1) the place-in-therapy of antidepressants; 2) recommended pediatric age(s) for starting antidepressant therapy; and c) recommendations for using 2 or more antidepressants simultaneously for the same condition in the pediatric population (multiple antidepressant therapy). Information about the key questions in the setting of depressive disorders are summarized in the following sections. Refer to **Table 2** for information from recent guidelines or guidance statements on the management of depressive disorders, with a focus on key questions 2 and 3.

6.2.1 Key Question 1: Guideline/Guidance Place-in-Therapy of Antidepressants for Pediatric Unipolar Depressive Disorders

Treatment of depressive disorders, particularly MDD, is guided by severity, treatment response, and sometimes, patient age. Treatment options typically include active support (eg, psychoeducation, monitoring, exercise), medications, and/or psychological interventions (eg, cognitive-behavioral therapy [CBT] or interpersonal therapy [IPT]).[16,18,127] Other non-pharmacologic treatments (eg, electroconvulsive therapy [ECT], repetitive transcranial magnetic stimulation [rTMS]) may be options for adolescents with severe or treatment-resistant depressive symptoms[16,31,127,128]; however, few US guidelines address using these treatments in youth. Particularly for rTMS, evidence as a treatment for youth is limited and its use is usually considered experimental.[16]

Generally, for mild depressive symptoms, active support[16,128,129] or psychological interventions[127] are usually recommended. Antidepressants, primarily SSRIs, as monotherapy or in combination with psychological therapy are usually recommended for moderate to severe depressive symptoms.[16,127-129]

Unlike some other guidelines, the AACAP (2023) guideline does not provide formal recommendations based on depression severity because recommendations are based on evidence from a single systematic review which did not consider disease severity. The AACAP endorses CBT or IPT as options for MDD or PDD treatment in children or adolescents, and SSRIs (preferably fluoxetine) with or without CBT as options for children or adolescents with MDD. Nonetheless, the AACAP acknowledges that despite the lack of evidence to drive a recommended treatment order, evidence-based psychotherapy and/or medications may be reserved for moderate to severe symptoms.[18]

When medications are recommended, many guidelines prefer fluoxetine as the first-line option due to it having the most robust evidence of benefits in children and adolescents.[16,18,31,127,128,130,131] Escitalopram is also a first-line option for adolescents (age ≥ 12 years) according to the 2018 US Guideline for Adolescent Depression in Primary Care (GLAD-PC).[129] The AACAP recommends not using the SSRI paroxetine due to evidence of increased suicidality (versus placebo) and adverse events on treatment withdrawal. Additionally, there is insufficient evidence to recommend treatment of MDD with SNRIs, TCAs or MAOIs in children or adolescents, according to the AACAP.[18] Due to safety concerns, the APA (2019) recommends against using clomipramine, imipramine, mirtazapine, paroxetine, or venlafaxine to treat MDD in adolescents. Furthermore, nefazodone was not addressed as a treatment option by the APA since it is not typically used in clinical practice due to safety concerns.[131] NICE (2019) recommends against using paroxetine, venlafaxine, or TCAs to treat depression in youth.[127] Although the optimal duration of antidepressant use is uncertain, they may be continued for a minimum of 6 months after symptom remission for an initial episode of MDD and for 12 months or longer among youth with severe or recurrent MDD.[18]

Few guidelines provide specific recommendations about use of antidepressants for depressive disorders other than MDD. Since several guidelines generally target "depression," it is unclear if recommendations are intended for non-MDD disorders.[31,129,130] Relative to evidence for the treatment of MDD, little evidence is available to guide treatment of pediatric PDD and DMDD.[16] Pharmacotherapy recommendations from the AACAP are specific to MDD; psychological therapies are recommended for treatment of PDD.[18] Fluoxetine or escitalopram are first-line pharmacotherapy options for treatment of PDD in children or adolescents (specific age undefined) according to Florida expert guidance.[16] For treatment of DMDD in children or adolescents, Korean expert guidance lists escitalopram or fluoxetine as first-line antidepressant options, while the Florida guidance considers antidepressants in combination with psychosocial therapy for youth (6-17 years old) a later-line treatment option.[132] When pharmacotherapy for DMDD is necessary, both Florida and Korean expert guidance also recommend other non-antidepressant medication options (eg, antipsychotics, mood stabilizers).[16,132]

Approximately 30-40% of children and adolescents do not respond fully to their initial treatment (SSRI or psychological).[133,134] Little evidence exists to guide management of treatment-resistant or unresponsive depression in children and adolescents.[18] In 2021, experts suggested working definitions for treatment-resistant depression (TRD) and treatment-refractory depression: TRD is persistent impairment despite appropriate trials of an evidence-based psychotherapy and evidence-based SSRI (ie, fluoxetine, escitalopram, or sertraline), and treatment-refractory depression meets criteria for TRD, with continued impairment despite a trial of 2 antidepressants (with at least 1 of the medication trials being an evidence-based SSRI). Response, partial response, and nonresponse to therapy are considered symptom reductions of ≥50%, 25-49%, and <25%, respectively.[134]

Overall, many pediatric depression treatment guidelines provide limited guidance for management of difficult-to-treat or TRD. This is likely due to the paucity of clinical trials in this population. The TORDIA (Treatment of Resistant Depression in Adolescents) RCT, which enrolled adolescents (12-18 years old) with moderately severe MDD despite at least 8 weeks of SSRI therapy (with at least 4 weeks at a dose equivalent to at least fluoxetine 40 mg daily), is the only rigorous RCT providing guidance after failure of initial SSRI therapy. In the TORDIA trial, the combination of switching to another medication (other SSRI or venlafaxine) with CBT resulted in superior treatment responses than switching medications alone; a different SSRI or venlafaxine showed similar response rates.[135] In another small trial among children with an insufficient response to 9 weeks of fluoxetine 20 mg daily, treatment response was higher (71%) among children who increased their fluoxetine dose to 40-60 mg daily than children who continued fluoxetine 20 mg daily (36% response).[134] Accordingly, US pediatric MDD guidelines other than Florida guidance, suggest considering SSRI dose increases, switching to another SSRI, and/or adding evidence-based psychotherapy when SSRI therapy alone is insufficient.[18,129] Florida guidance also suggests switching to alternative SSRIs and/or adding psychotherapy, while also providing additional guidance for next steps if those options are insufficient, including switching to other antidepressant monotherapy, augmenting SSRI therapy, or ECT as last-line therapy for severe/psychotic MDD in adolescents.[16]

6.2.2 Key Question 2: Guideline or Expert Guidance Recommendations for Age to Receive an Antidepressant for Depressive Disorders

Of 11 recent (2018-2023) US or international guidelines or expert opinion guidance statements addressing the management of pediatric depression, 6 provide recommendations regarding the specific ages for initiating pharmacotherapy.[16,127,129-132] Several other guidelines are less specific by generally targeting recommendations for children and adolescents.[31,128,136] AACAP (2023) pharmacotherapy recommendations for pediatric MDD target children (except very young children) and adolescents generally, with the additional guidance that RCT evidence used to make the recommendations usually included children ages 7-11 years old and adolescents ages 11-12 to 18 years.[18] The Maudsley prescribing guidelines (2021) also did not provide specific ages for recommendations for children and adolescents, but elaborated that fluoxetine and escitalopram are FDA-approved for treatment of youth ≥ 8 years old or ≥ 12 years old, respectively.[31]

Of the guidelines that provided specific ages within their pharmacotherapy recommendations (in general), the Florida guidance (2022) has the youngest age for medication use (4 years old).[16] Two other guidelines (Korean societies expert consensus, 2021 and NICE, 2019) consider pharmacotherapy as an option for children as young as 5 years old.[127,132] Nonetheless, evidence for using antidepressants in children less than 6[16] to 7 years old[137] is very limited. The APA (2019) declined making pharmacotherapy recommendations for children 6-12 years old (providing recommendations for age 13-18 only) due to insufficient evidence for using antidepressants in children.[131] NICE weakly recommends fluoxetine (with psychotherapy) for children 5-11 years old with moderate to severe depression who fail psychotherapy, though they pointed out that fluoxetine efficacy is not established in this age group.[127]

Most guidelines providing pharmacotherapy guidance for treatment of MDD in children under 6 years old recommend treatment with fluoxetine in combination with psychosocial therapy. Per guidance from Gleason et al (2007) on treatment of MDD in pre-school age children, fluoxetine with concurrent psychotherapy is a later-line option for children *without* a comorbidity treatable with a medication that

has relatively greater evidence for use in very young children (eg, ADHD), and severe symptoms despite appropriate trials of psychotherapy alone.[27] Fluoxetine is recommended by Gleason et al based upon evidence for its use in older children.[27] Similarly, NICE recommends offering fluoxetine treatment for moderate-severe depression only in combination with psychological therapy for youth 5-18 years, though if desired, the youth may opt for treatment with medication only.[127] Florida guidance also recommends considering combining fluoxetine with psychosocial treatment when treating youth 4 to <6 years old with severe symptoms and insufficient response to psychosocial treatment alone.[16]

Several guidelines addressing treatment of MDD in very young children (<6 years old) recommend for certain antidepressants and against others:

- Most guidelines specifically recommend treatment with fluoxetine when pharmacotherapy is appropriate.[16,27,127]
- According to the NICE guideline, sertraline or citalopram are later-line options for children as young as 5 years old who have severe symptoms and fail an appropriate trial of fluoxetine and psychological therapy.[127]
- Only the Korean depression expert guidance considers escitalopram (for mild to severe symptoms) or sertraline (for severe symptoms) to be first-line pharmacotherapy options along with fluoxetine, for children as young as 5 years old.[132]
- Use of bupropion is recommended against in pre-school aged children by Gleason et al (as of 2007) due to a lack of evidence for use and seizure risks in youth with a developing nervous system.[27] TCAs are recommended against use in pre-school aged children by Florida guidance and Gleason et al[16,27]; Florida guidance also recommends against using paroxetine in this age group.[16]

6.2.3 Key Question 3: Guideline or Review Guidance about Multiple Antidepressant Therapy (MAT) for Depression

Based on recent clinical practice guidelines and expert opinion guidance statements addressing treatment of pediatric depression, there appears to be little evidence for using multiple antidepressants to treat children or adolescents. **The few guidelines/guidance statements recognizing MAT as an option, suggest it only in the setting of persistent symptoms despite treatment with 1-2 adequate trials of SSRI therapy with or without evidence-based psychotherapy**.[16,130,132] According to the AACAP (2023), there is insufficient evidence to guide combined antidepressant therapy.[18]

Despite the paucity of evidence for MAT to treat depressive disorders in pediatric patients, expert guidelines from the Florida best practices group (2022), Korean psychiatric organizations (2021), and Indian Psychiatric Society (2019) recognize it as an option.[16,130,132] Little detail is provided by Korean expert consensus other than combined treatment with 2 antidepressants is a possible second-line option for children with mild to severe MDD (with a lack of consensus for severe psychotic MDD), or adolescents with mild to severe MDD (with a lack of consensus).[132] Both Florida and Indian Psychiatric Society guidance suggest the option of augmenting SSRI therapy with another medication based on extrapolation of evidence from adults.[16,130] Only Florida specifies antidepressants to be combined with an SSRI based on adult evidence – **bupropion or mirtazapine**.[16] Notably, these guidelines and several other reviewed guidelines also mention the option to augment SSRI therapy with non-antidepressants in place of or as an alternative to antidepressant augmentation. Other medications considered an option

for augmenting SSRI therapy by at least 1 pediatric guideline/consensus article are second-generation antipsychotics, lithium, buspirone, thyroxine, lamotrigine, or triiodothyronine (the augmentation strategy varies by guideline/consensus article).[16,31,130,138]

Other expert guidance (Dwyer et al, 2021) recognizes SSRI augmentation with another antidepressant as one of several unproven options for adolescent treatment-refractory depression (ie, after failure of ≥ 2 different SSRIs and evidence-based psychotherapy).[134] **Since evidence is limited,[16,130] Dwyer et al emphatically suggests that these options should only be considered after confirming true treatment resistance (including compliance with tried therapies) and accuracy of the depression diagnosis**. *Using adult evidence as guidance*, Dwyer et al suggests MAT (or an alternative agent) as an augmentation option for treatment refractory depression, especially when the adolescent has a partial but incomplete response to SSRI monotherapy ± psychotherapy. Augmentation strategies with the highest level of evidence (Level A, evidence from a RCT or meta-analysis of RCTs) in *adults* are antipsychotics, lithium, and psychostimulants. Augmentation with bupropion is graded as level B evidence (evidence from a non-controlled clinical trial) and an evidence grade for mirtazapine was not provided by Dwyer et al, despite recognizing both antidepressants as evidence-based augmentation strategies.[134] Notably, in adult clinical trials for non-responders to 1 or more therapies, combination therapy with bupropion or mirtazapine and other antidepressants was studied as acute treatment (eg, 4-12 weeks).[139] The recommended duration for combination antidepressant therapy in children or adolescents with resistant depression is unclear.

In adults, and presumably adolescents, adding bupropion (a dopamine/norepinephrine reuptake inhibitor) or mirtazapine (a noradrenergic and presynaptic alpha-2 auto-receptor antagonist)[128,139] to SSRIs is suggested as a rational strategy due to differing and possibly complementary mechanisms of action.[139,140] However, combining 2 antidepressants with strong serotonergic activity (ie, SSRIs, SNRIs, clomipramine, MAOIs, and possibly mirtazapine) should not be done or performed cautiously.[140] While temporary overlap between antidepressants (ie, cross-tapering) may be used cautiously when switching between antidepressants,[130] concurrent use of SSRIs and MAOIs including when cross-tapering is contraindicated due to the risk of serotonin syndrome.[18,129]

6.2.3.1 Other References to MAT by Expert Opinion Reviews

No systematic reviews were identified from a supplemental literature search for reviews addressing MAT for treating depressive disorders. Evidence summarized below is from non-systematic reviews, which incidentally mentioned MAT. Reviewed pediatric evidence for MAT is limited to observational or descriptive data. RCT-level evidence is limited to *post-hoc* evidence, which is observational or descriptive in nature since no study randomized participants to treatment with MAT versus an alternative therapy. The following bullets summarize additional MAT information from expert reviews.

- **Trazodone** was used as a sleep aid in combination with SSRI therapy (paroxetine or fluoxetine) at the discretion of the treating provider among at 33 adolescent patients during a RCT for MDD comparing switching to another SSRI, venlafaxine, and adding CBT. Notably, in a *post-hoc* analysis, patients who received trazodone were less likely to respond to SSRI ± CBT than patients who received an alternative sleep aid.[141] It is unclear whether the lower response rate is due to unassessed confounding factors associated with the patients selected to receive trazodone, or some other mechanism (eg, drug interaction between trazodone and SSRIs).[134,141] Expert opinion reviews

(published in 2006 and 2012) mention trazodone as an option to be added to SSRI therapy in youth with depression who experience insomnia as a side effect of SSRI therapy (to be used in girls specifically),[142] or as brief initial adjunctive therapy with an SSRI in youth presenting with insomnia associated with depression.[24] No empirical evidence is cited to support adding trazodone to an SSRI for treating youth with depression,[24,142] other than the *post-hoc* analysis of the trial described above, which was used to emphasize caution when adding trazodone to SSRI therapy.[24]

- **Mirtazapine** is suggested by experts (in 2006) as a sleep aid for adolescents to be added to effective SSRI therapy that is disturbing sleep despite non-pharmacologic treatment. No empiric evidence to support adding mirtazapine was provided.[142] Notably, in 2023, an expert questioned the practice of mirtazapine *augmentation* (ie, adding to partially effective SSRI/SNRI monotherapy) to treat depressive symptoms in **adults** due to evidence being limited to 1 very small (<30 patients) RCT sponsored by the mirtazapine manufacturer, and a larger RCT that failed to show a clinically significant benefit over placebo augmentation. Slightly more robust *adult* evidence does support using mirtazapine as *combination therapy* with an SSRI (ie, when the SSRI and mirtazapine are started together in people who have not already failed monotherapy with that SSRI).[143]
- **Bupropion** is an option for augmentation of SSRI therapy in adolescents with TRD or an insufficient response to initial antidepressant therapy, primarily based on evidence from **adults**,[144] according to expert opinion reviews.[24,145] As of 2012, there was a lack of systematic studies of bupropion augmentation in adolescents with depression.[24,145] Evidence for bupropion therapy in adolescents as of 2011 was limited to 2 small single-arm open-label trials suggesting the efficacy of bupropion sustained released monotherapy for depressive symptoms in adolescents (ages 11-17) with MDD,[146] or MDD/dysthymia with comorbid ADHD.[147]
- **Intranasal esketamine** is FDA-approved for treatment of resistant and suicidal depression in **adults**, for whom it is used in combination with standard oral antidepressants.[148,149] An RCT investigating the impact of esketamine versus control (midazolam), both in combination with standard oral antidepressant therapy (eg, fluoxetine, escitalopram, or sertraline), in children and adolescents (9-17 years old) with MDD at risk for suicide has been completed, but results are not yet published.[150]
- **Intravenous ketamine** (0.5 mg/kg) has been administered to adolescents (ages 13-18) with treatment-resistant MDD receiving stable doses of an oral antidepressant for at least 4 to 8 weeks before starting ketamine.[151,152] In an open-label, single-arm trial (with 6 ketamine infusions given over 2 weeks), patients were on stable regimens including an SNRI (5 patients), bupropion (2 patients), or SSRI (2 patients); and one 16-year-old patient's regimen included bupropion and an SSRI.[153] In a second cross-over trial of single ketamine versus midazolam infusion, some adolescents (13-17 years old) were receiving SSRI therapy (9 patients), SNRI or mirtazapine therapy (7 patients), and SSRI-SNRI combination therapy (1 patient).[151] In the single arm trial, about 40% of patients achieved clinical response after ketamine treatment, and in the cross over trial, ketamine was significantly more effective than midazolam for depression symptoms. Combining information from both trials, ketamine-associated side effects included dissociation, nausea, transient blood pressure and heart rate changes, and worsened suicidal ideation (in 1 patient).[149] No information about potential differences in ketamine tolerability or efficacy in patients receiving concomitant oral antidepressants was provided by publications for both trials.[151 152] Two case reports also describe effective treatment of 2 adolescents (14 and 15 years old) with TRD without sequelae using intravenous ketamine concurrently with oral antidepressant therapy.[154-156]

Table 2. Pediatric Depression Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
American Academy of Child & Adolescent Psychiatry (AACAP); 2023[18] *Target pediatric population(s): Children (except for very young children) or adolescents with MDD and/or PDD[b].*	
• **SSRIs (except paroxetine), with fluoxetine preferred, are options for *children* and *adolescents* with MDD** (2I) ○ Guideline does not explicitly define a minimum age for starting pharmacotherapy ○ Recommendation is based on RCT/CCT evidence from a single SR; among the SR studies (addressing ≥ 6-week pharmacologic or nonpharmacologic treatments), "children" usually meant ages 7-11 years and "adolescent" usually meant ages 11-12 to 18. Most evidence included adolescents. Youngest age in at least 1 RCT/CCT per agent[137]: ▪ SSRIs: fluoxetine, 7 years (combined with CBT, 12 years); escitalopram, 6 years; citalopram, 7 years; paroxetine, 7 years; vilazodone, 12 years ▪ SNRIs: duloxetine, 11 years; desvenlafaxine, 7 years; venlafaxine ER: mean age, 12.2 years; venlafaxine with therapy, 8 years ▪ TCAs: imipramine, 12 years; nortriptyline, 5 years; desipramine, 13 years; amitriptyline, 12 years ▪ MAOI: selegiline TD, 12 years	• Other than brief combined use when switching between medications, the guideline does not mention situations to combine antidepressants. ○ The combination of fluoxetine with CBT is a recommended (2I) option for children or adolescents with MDD ○ There is little evidence to guide therapy for TRD. Switching to another SSRI, or sometimes, dose-increases of the initial SSRI, are options. Over half of nonresponding adolescents (to a SSRI course) with MDD exhibited a response after switching to another SSRI or SNRI combined with CBT in one study. • **There is insufficient evidence for combined use of medications.** • MAOIs should not be used with another serotonergic drug to avoid serotonin syndrome. ○ The combination of an MAOI and SSRI is <u>contraindicated</u>
Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents–Major Depressive Disorder section; 2022[16] *Target pediatric population(s): Children and adolescents with MDD, PDD, or DMDD. For MDD, treatment recommendations are provided specifically for age <6 years and ages 6-17 years.*	
<u>MDD treatment:</u> • Antidepressant options **for children <4 years old:** ○ No antidepressant-specific options provided. Generally, medications (monotherapy at the lowest possible dose is preferred) should only be used after an insufficient response to psychosocial therapies once the diagnosis is confirmed and the potential benefits are considered to outweigh the risks (level 2 for all mental health conditions). • Antidepressant options **for children 4 to <6 years old; "**Clinicians should realize that data below the age 6 for treating major depressive disorder is extremely limited. Caution in using pharmacological treatment below age 6 is warranted" (page 54): ○ For severe symptoms, fluoxetine in combination with psychosocial therapy is an option (level 2) for **children 4-5 years old** with an unsatisfactory response to psychosocial therapy • Antidepressant options **for children 6-17 years:** ○ Fluoxetine as monotherapy or in combination with psychotherapy is an option (level 2a) for treatment of moderate to severe symptoms or for mild MDD that insufficiently responded to evidence-based psychosocial interventions. Combination treatment (fluoxetine with CBT or IPT) is recommended for moderate to severe symptoms.	• **Augmentation of an SSRI with the antidepressant bupropion or mirtazapine** (or alternatively, thyroxine, lithium, buspirone, aripiprazole, quetiapine, or risperidone) is an option (level 5a) for MDD treatment in youth 6-17 years old, after failure of other recommended options. ○ Evidence for these combinations is extrapolated from adult only data

[a] *AAACP formal recommendations: <u>strength 2</u> = there is uncertainty about whether the benefits outweigh the risks; <u>evidence I</u> = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes*

APA formal recommendations: are based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

GLAD-PC <u>Evidence levels:</u> Assigned per the Oxford Center for Evidence-Based Medicine criteria, 1= SR of RCTs or n-of-1 trials; <u>Very strong</u> = >90% expert agreement of steering group members

RANZCP <u>Evidence levels:</u> Evidence-based recommendation (EBR) level II (EBR II) = RCT evidence

NICE <u>recommendation strength:</u> <u>Offer</u>: generally, indicates strong recommendation for the intervention; <u>Should not use</u>: generally, indicates a strong recommendation <u>against</u> the intervention; <u>Consider</u>: generally, indicates a weak recommendation for the intervention, meaning that the intervention should be used for some patients if the benefits are considered to outweigh the risks.

[b] *PDD is a DSM-recognized diagnosis for chronic depression (≥ 1 year) that incorporates previous DSM features for MDD and dysthymia.*

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; DMDD, disruptive mood dysregulation disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ER, extended release; FDA, Food and Drug Administration; GLAD-PC, Guidelines for Adolescent Depression in Primary Care; IPT, interpersonal therapy; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; PDD, persistent depressive disorder; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT(s), randomized controlled trial(s); SSRI(s), selective serotonin reuptake inhibitor(s); SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SR(s), systematic review(s); TCA(s), tricyclic antidepressant(s); TD, transdermal; TRD, treatment-resistant depression; UK, United Kingdom

Table 2. Pediatric Depression Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
○ Escitalopram is an option (level 2b) for **ages ≥ 12 years.** ○ After failure of monotherapy with both SSRIs recommended in level 2, confirmation of the diagnosis, and intensification of prior treatments (eg, increased dose of medication) with poor response, the following antidepressants are options: ▪ Sertraline, citalopram, bupropion, or venlafaxine (level 5a) ▪ Augmentation of an SSRI with bupropion or mirtazapine (among other options) (level 5a) • Antidepressants **NOT recommended for MDD treatment for age <6 years**: TCAs or paroxetine; no antidepressant is recommended as monotherapy without concurrent psychosocial treatment • Antidepressants **NOT recommended for MDD treatment for age 6-17 years**: paroxetine as a 1st- or 2nd-line option PDD treatment (**no age specified**): consider fluoxetine or escitalopram first-line (few studies are available in this population) DMDD treatment (ages 6-17 years): Since this is newly established diagnosis in DSM-5, there is little evidence to guide treatment. Medications (antidepressants, or others like mood stabilizers or antipsychotics) targeted toward aggression symptoms are options for youth with moderate to severe DMDD, but they should only be used in combination with psychosocial treatments.	
The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition – Ch. 5 Children and Adolescents; 2021[31] *Target pediatric population(s): Children and adolescents with depression.*	
• When medications are indicated (usually for moderate-severe depression or when psychotherapy is inaccessible), **fluoxetine, FDA-approved for age 8+, is a first-line option.** Second-line options are sertraline or citalopram, and a third-line option is escitalopram, FDA-approved for age 12+. Fourth-line options (all based on adult evidence), generally used if response to prior therapies has been inadequate, includes augmentation of an antidepressants with a second-generation antipsychotic or lithium, or mirtazapine if sedation is needed. ○ **Greater caution using antidepressants in children may be warranted, since there is comparatively little evidence for use of antidepressants compared to adolescents.** • Alternative treatments, generally reserved for last-line options or for severe disease, are esketamine, electroconvulsive therapy, or repetitive transcranial magnetic stimulation. **However, these are not recommended options for very young children** (age not specified)**.** • **"There has been no research investigating antidepressant use in pre-school children, and medications are not recommended for this age group"** (page 545)	• **No information provided about combined antidepressants in children or adolescents.** • Other augmentation strategies, including combining lithium or a second-generation antipsychotic with an antidepressant, are recommended later-line pharmacotherapeutic options based on evidence from adults. • Antidepressant combinations considered options for adults with treatment resistant depression include an SSRI and bupropion, or an SSRI or venlafaxine and mirtazapine (among other options for difficult-to-treat cases).[157]
Korean College of Neuropsychopharmacology and Korean Society for Affective Disorders Expert Consensus; 2021[132] *Target pediatric population(s): Pharmacologic treatment options for children (elementary school-aged, about 5-12 years) or adolescents (middle- and high-school-aged, about 13-17 years) with MDD, or children and adolescents (inferred as approximately ages 5-17 years) with DMDD.*	
• For **children and adolescents with DMDD**, antidepressants as monotherapy or in combination with an atypical antipsychotic are among second-line treatment options (no first-line option was provided) • Preferred first-line antidepressants are **escitalopram or fluoxetine**, whereas sertraline, bupropion, and duloxetine are second-line options.	• The **combination of 2 antidepressants is listed as a second-line treatment option** for children with mild-severe MDD (with a lack of consensus for severe psychotic MDD), and adolescents with mild-severe MDD (with a lack of consensus for all assessed conditions, including mild-moderate, severe, and severe psychotic MDD).

[a] *AAACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes*

APA formal recommendations: are based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

GLAD-PC Evidence levels: Assigned per the Oxford Center for Evidence-Based Medicine criteria, 1= SR of RCTs or n-of-1 trials; Very strong = >90% expert agreement of steering group members

RANZCP Evidence levels: Evidence-based recommendation (EBR) level II (EBR II) = RCT evidence

NICE recommendation strength: Offer: generally, indicates strong recommendation for the intervention; Should not use: generally, indicates a strong recommendation against the intervention; Consider: generally, indicates a weak recommendation for the intervention, meaning that the intervention should be used for some patients if the benefits are considered to outweigh the risks.

[b] *PDD is a DSM-recognized diagnosis for chronic depression (≥ 1 year) that incorporates previous DSM features for MDD and dysthymia.*

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; DMDD, disruptive mood dysregulation disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ER, extended release; FDA, Food and Drug Administration; GLAD-PC, Guidelines for Adolescent Depression in Primary Care; IPT, interpersonal therapy; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; PDD, persistent depressive disorder; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT(s), randomized controlled trial(s); SSRI(s), selective serotonin reuptake inhibitor(s); SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SR(s), systematic review(s); TCA(s), tricyclic antidepressant(s); TD, transdermal; TRD, treatment-resistant depression; UK, United Kingdom

Table 2. Pediatric Depression Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
• For **children with mild-moderate MDD:** antidepressant monotherapy is the treatment-of-choice, with first-line options being **escitalopram or fluoxetine**. Second-line antidepressants are sertraline, bupropion, duloxetine, or paroxetine (with a lack of consensus for this agent). • For **children with severe MDD:** antidepressant monotherapy or in combination with an atypical antipsychotic are first-line treatment options; the combination is the treatment-of-choice for severe psychotic MDD. **First-line antidepressants are escitalopram (the treatment-of-choice for non-psychotic cases), fluoxetine, or sertraline**. Second-line antidepressants are bupropion, paroxetine (with a lack of consensus), duloxetine (with a lack of consensus), venlafaxine (with a lack of consensus for psychotic MDD), desvenlafaxine (with a lack of consensus), or mirtazapine (for psychotic MDD only). • For **adolescents with mild-moderate MDD:** antidepressant monotherapy is a first-line option, with **escitalopram being the treatment-of-choice. Fluoxetine and sertraline are other first-line options**. Second-line antidepressant options with consensus are venlafaxine. Other second-line antidepressant options without consensus are duloxetine, bupropion, paroxetine, desvenlafaxine, agomelatine, vortioxetine, and mirtazapine. • For **adolescents with severe MDD:** first-line options are antidepressant monotherapy or the combination of an antidepressant and atypical antipsychotic (the treatment-of-choice for psychotic MDD). **First-line antidepressants are escitalopram (the treatment-of-choice for psychotic and non-psychotic MDD), fluoxetine (also a treatment-of-choice for non-psychotic MDD), and sertraline**. Second-line antidepressants with consensus are venlafaxine or bupropion (for non-psychotic MDD only). Other second-line antidepressants without consensus are paroxetine, duloxetine, desvenlafaxine, agomelatine (for non-psychotic MDD only), vortioxetine, and mirtazapine (for psychotic MDD only)	**However, no information is provided about which antidepressants may be combined.**
Royal Australian and New Zealand College of Psychiatrists (RANZCP); 2020[128] *Target pediatric population(s): Children and adolescents (no specific target age range) with MDD*	
• **Fluoxetine** monotherapy or in combination with psychological interventions is an option for moderate-severe MDD in children and adolescents (**no age specified**). (EBR II) Active monitoring is recommended first-line for children and adolescent with mild MDD. (consensus recommendation) • Other SSRIs or a non-SSRI agent (no agent/class specified) are other options for unresponsive MDD	• **No information provided about antidepressant combination therapy.** Augmentation of an antidepressant with a mood stabilizer or psychological therapy are recommended options for unresponsive MDD in children and adolescents. (EBR II)
American Psychological Association (APA); 2019[131] *Target pediatric population(s): Adolescents (defined as ages 13-18 years) with MDD, PDD or subsyndromal depression.*	

• **Due to insufficient evidence, no formal recommendations for psycho- or pharmaco-therapies were provided for children (defined as ages 6-12 years)**
• **Fluoxetine is a recommended initial treatment option for *adolescents* with MDD**
• **The following medications are recommended *against* for most *adolescents* with MDD due to safety concerns:**
  ○ Clomipramine, imipramine, mirtazapine, paroxetine, venlafaxine
  ▪ Paroxetine is preferred over clomipramine or imipramine if it is necessary to use one of those medications (no information is available for other comparisons)
• No recommendations were provided for use of nefazodone for depression, "…given its lack of clinical relevance for current practice (i.e., expert psychiatrist indicate that this medication is almost never used for children or adolescent care due to significant side effects) (page 38)"[131]
	• **No information was provided about the combination of medications to treat depression in children or adolescents**
	• Augmentation of an antidepressant with another antidepressant is conditionally recommended as an option for adults with an insufficient response to initial antidepressant therapy; however, no specific antidepressant augmentation combinations were provided.

[a] *AAACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes*

APA formal recommendations: are based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

GLAD-PC Evidence levels: Assigned per the Oxford Center for Evidence-Based Medicine criteria, 1= SR of RCTs or n-of-1 trials; Very strong = >90% expert agreement of steering group members

RANZCP Evidence levels: Evidence-based recommendation (EBR) level II (EBR II) = RCT evidence

NICE recommendation strength: Offer: generally, indicates strong recommendation for the intervention; Should not use: generally, indicates a strong recommendation against the intervention; Consider: generally, indicates a weak recommendation for the intervention, meaning that the intervention should be used for some patients if the benefits are considered to outweigh the risks.

[b] *PDD is a DSM-recognized diagnosis for chronic depression (≥ 1 year) that incorporates previous DSM features for MDD and dysthymia.*

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; DMDD, disruptive mood dysregulation disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ER, extended release; FDA, Food and Drug Administration; GLAD-PC, Guidelines for Adolescent Depression in Primary Care; IPT, interpersonal therapy; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; PDD, persistent depressive disorder; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT(s), randomized controlled trial(s); SSRI(s), selective serotonin reuptake inhibitor(s); SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SR(s), systematic review(s); TCA(s), tricyclic antidepressant(s); TD, transdermal; TRD, treatment-resistant depression; UK, United Kingdom

Table 2. Pediatric Depression Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
National Institute for Health and Care Excellence (NICE); 2019 *Target pediatric population(s): Children and adolescents **ages 5-18 years** with depression. Strength of recommendations is reflected in the wording of recommendations.*[158]	
• For mild depression symptoms or dysthymia in youth, non-pharmacotherapy strategies are recommended first-line. "Antidepressant medication should not be used for the initial treatment of children and young people with mild depression" (page 49) • For moderate-severe depression in youth 5-18 years old, psychological therapies with or without fluoxetine are treatment options. In the UK, fluoxetine is approved for youth aged 8-18 years. The type of psychological therapy recommended differs between children 5-11 and youth 12-18 due to differences in the evidence. ○ The **combination of fluoxetine and psychological therapies may be considered for youth 12-18 years old presenting with moderate-severe depression** instead of psychological therapy followed by combination treatment. ○ **Offer fluoxetine to youth 12-18 years old with moderate-severe depression despite 4-6 sessions of evidence-based therapy.** ○ **For children 5-11 years with moderate-severe depression that failed to respond to psychological therapy (4-6 sessions), therapy with fluoxetine can be considered cautiously**. Evidence for using fluoxetine in this younger age group is not established. • Antidepressants should always be offered in combination with psychological therapy. • **Fluoxetine is the preferred antidepressant for all youth. Second-line antidepressants are citalopram or sertraline.** • Select antidepressants/drug classes **"should not be used"** to treat depression **in youth** include **paroxetine, venlafaxine, or tricyclic antidepressants**	• **No information provided about antidepressant combination therapy.** • The combination of an SSRI and psychological therapy is a recommended treatment option for children and adolescents. • Antidepressant therapy augmentation with a second-generation antipsychotic may be considered for psychotic depression
Royal College of Psychiatrists Position Statement; 2019[136] *Target pediatric population(s): Children and adolescents (age limits are not defined). Focus of the statement is use of antidepressants to treat depression as recommendations for future actions by policymakers to improve antidepressant prescribing.*	
• The College endorses a statement by NICE (2005), indicating antidepressants are a second-line treatment option for *children* or *adolescents* with moderate-severe depression with an insufficient response to psychotherapy, or as a first-line option for severe depression treated by a specialist. ○ No information is provided about an exact target age.	• No information provided
British Association of Psychopharmacology (BAP)–Expert Opinion Response to Common Practical Questions; 2022[138] *Targe pediatric population(s):* Children and adolescents (specific ages not defined).	
• Little information is provided about ages for antidepressant therapy in children and adolescents except that for adolescents near 18 years old with TRD, non-SSRI antidepressants with positive evidence in adults (eg, mirtazapine and venlafaxine) may be considered	• No information provided about combination antidepressants. There is a paucity of evidence to guide treatment after failure of evidence-based SSRIs or psychotherapy ○ For TRD with failed response to evidence-based treatments of an appropriate intensity and duration, antidepressant augmentation with other agents shown to be efficacious in adults (ie, lamotrigine, atypical antipsychotic, lithium, or L-thyroxine) can be considered

[a] *AAACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes*

APA formal recommendations: are based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

GLAD-PC Evidence levels: Assigned per the Oxford Center for Evidence-Based Medicine criteria, 1= SR of RCTs or n-of-1 trials; Very strong = >90% expert agreement of steering group members

RANZCP Evidence levels: Evidence-based recommendation (EBR) level II (EBR II) = RCT evidence

NICE recommendation strength: Offer: generally, indicates strong recommendation for the intervention; Should not use: generally, indicates a strong recommendation against the intervention; Consider: generally, indicates a weak recommendation for the intervention, meaning that the intervention should be used for some patients if the benefits are considered to outweigh the risks.

[b] *PDD is a DSM-recognized diagnosis for chronic depression (≥ 1 year) that incorporates previous DSM features for MDD and dysthymia.*

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; DMDD, disruptive mood dysregulation disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ER, extended release; FDA, Food and Drug Administration; GLAD-PC, Guidelines for Adolescent Depression in Primary Care; IPT, interpersonal therapy; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; PDD, persistent depressive disorder; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT(s), randomized controlled trial(s); SSRI(s), selective serotonin reuptake inhibitor(s); SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SR(s), systematic review(s); TCA(s), tricyclic antidepressant(s); TD, transdermal; TRD, treatment-resistant depression; UK, United Kingdom

Table 2. Pediatric Depression Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
Indian Psychiatric Society; 2019[130] *Target pediatric population(s): Children and adolescents (no age specified).*	
• Antidepressants are a treatment option when preferred by the child/guardian and are usually a treatment of choice for depression that failed to respond to psychotherapy, lack of access to psychotherapy with moderate depressive symptoms, or severe depression. ○ **SSRIs, especially fluoxetine, are first line for children ≥ 8 years old**. Alternative SSRIs are escitalopram or sertraline. (non-graded statements) • After failure of 2 adequate trials of antidepressants, switching to venlafaxine, bupropion, or mirtazapine are suggested options for children and adolescents based on positive adult data. Providers should verify the patient's antidepressant compliance and psychotherapy adequacy and ensure the correct diagnosis before starting one of these agents. • It is noted that the following antidepressants have been evaluated in children and adolescents, with most antidepressants not demonstrating efficacy: imipramine, desipramine, clomipramine, nortriptyline, amitriptyline, fluoxetine, paroxetine, escitalopram, sertraline, duloxetine, venlafaxine, nefazodone, and mirtazapine. Meta-analyses have demonstrated the efficacy of fluoxetine for children and adolescents with depression.	• Cross-tapering is a preferred strategy for switching between antidepressants when a patient has been taking an antidepressant already • **Augmentation of an SSRI with CBT or possibly another medication with evidence for combined use in adults is an option** for children and adolescent who partially respond to SSRI monotherapy. No specific augmenting agent is recommended. • **For TRD, antidepressant augmentation (no specific agent suggested) or combination with other agents (eg, lithium, or triiodothyronine**) are options for children and adolescents, among others.
Guidelines for Adolescent Depression in Primary Care (GLAD-PC); 2018[129,159] *Target pediatric population(s): **Adolescents ages 10-21 years** (range of ages that may be developmentally adolescent). Ages 18-21 may be treated as an adolescent or an adult, depending on developmental status.[14]*	

• Evidence-based treatments including certain psychotherapies and/or antidepressants are recommended for indicated **adolescents** (1, very strong)
  ○ Adolescents with mild symptoms may undergo active monitoring for 6-8 weeks before treatment, whereas psychotherapy and/or medication are recommended initial treatments for moderate-severe symptoms.
  ○ **SSRIs, especially fluoxetine or escitalopram for age 12+, are recommended first-line medications.**
  ▪ Listed SSRI options with RCT level evidence are fluoxetine, escitalopram, citalopram, sertraline, and paroxetine. Paroxetine should only be started in non-primary care settings.
  ▪ Another SSRI listed as an option, but apparently without RCT evidence, is fluvoxamine
• Use of older antidepressants (ie, MAOIs or TCAs) was specially not addressed by the guideline since they are not readily used in clinical practice due to a lack of efficacy in clinical trials
	• **No specific recommendations about combining antidepressants**
	• Combined use of SSRIs and MAOIs is contraindicated
	• Options for partial treatment and/or no treatment response are combining medication with psychotherapy, using the maximally tolerated medication dose, and/or switching to another antidepressant
	  ○ It is noted that "A doctor should also re-evaluate the diagnosis and consider a combination of medication if a child fails 3 medication trials" (page 94)[159]

[a] AAACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes

APA formal recommendations: are based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

GLAD-PC Evidence levels: Assigned per the Oxford Center for Evidence-Based Medicine criteria, 1= SR of RCTs or n-of-1 trials; Very strong = >90% expert agreement of steering group members

RANZCP Evidence levels: Evidence-based recommendation (EBR) level II (EBR II) = RCT evidence

NICE recommendation strength: Offer: generally, indicates strong recommendation for the intervention; Should not use: generally, indicates a strong recommendation against the intervention; Consider: generally, indicates a weak recommendation for the intervention, meaning that the intervention should be used for some patients if the benefits are considered to outweigh the risks.

[b] PDD is a DSM-recognized diagnosis for chronic depression (≥ 1 year) that incorporates previous DSM features for MDD and dysthymia.

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; DMDD, disruptive mood dysregulation disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ER, extended release; FDA, Food and Drug Administration; GLAD-PC, Guidelines for Adolescent Depression in Primary Care; IPT, interpersonal therapy; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; PDD, persistent depressive disorder; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT(s), randomized controlled trial(s); SSRI(s), selective serotonin reuptake inhibitor(s); SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SR(s), systematic review(s); TCA(s), tricyclic antidepressant(s); TD, transdermal; TRD, treatment-resistant depression; UK, United Kingdom

6.3 Anxiety Disorders

Anxiety disorders are characterized by persistent, excessive worry about future events that significantly impairs daily functioning.[11] Key symptoms of anxiety disorders are hyperarousal, avoidance, and distorted thoughts (eg, "what if" statements) about worries; some youth also present with somatic complaints like muscle tension.[160] Separation anxiety disorder, selective mutism, specific phobias, social anxiety disorder (SAD), panic disorder (PD), agoraphobia, and generalized anxiety disorder (GAD) are types of anxiety disorders recognized by the DSM-5-TR, among others.[11] Youth may meet criteria for more than one anxiety disorder concurrently.[12] The clinical course for anxiety varies–certain youth experience fluctuating symptoms, some attain complete remission, and other may achieve remission of one anxiety disorder only to manifest symptoms of another anxiety disorder in the future.[160] The prevalence of many anxiety disorders declines by later adulthood, possibly indicating that the severity improves with time. [12] Nonetheless, anxiety disorders may impair normative social development, and early intervention during childhood may prevent persistence of these symptoms into adulthood.[31] Approximately two-thirds of youth demonstrate sustained responses to treatment.[161]

As a group, anxiety disorders are the most frequent mental health diagnosis in youth.[160,162] In the US, approximately 9.4% of surveyed youth (3-17 years old) endorsed ever having anxiety problems and 7.8% endorsed ongoing anxiety problems. Anxiety disorders tend to increase in prevalence with age, with youth 12-17 years experiencing anxiety symptoms at higher rates than children ages 6 to 11 or 3 to 5 years (rates of anxiety are only 2% in this latter age group).[2]

Below is a description of major anxiety disorders occurring in youth, listed in order of the earliest typical age of onset.

- *Separation anxiety*: Youth with separation anxiety experience excessive worry/distress about separation from someone (eg, a caregiver).[12,160] This disorder may present as early as preschool age; estimated past year prevalence is higher in children (4%) than adolescents (1.6%). GAD and specific phobias commonly co-occur with separation anxiety disorder.[12]
- *Selective mutism*: Youth with selective mutism are unable to speak in some but not all situations with impairment unattributable to a lack of language skills.[12,160] This disorder is uncommon (estimated prevalence of 0.03-1.9%) and less is known about the longitudinal course of the disorder.[12] Often, it presents in preschool age children, and rarely in adolescents.[12,160] Social anxiety disorder is a very common comorbidity.[12]
- *Specific phobias*: Youth with specific phobias worry about one or more specific things (eg, animals) or situations (eg, medical procedures).[12,160] More than one phobia is common. Usually, this disorder presents in early school age children (mean age of 10 years), with an estimated prevalence of about 5% in children and 16% in adolescents. Psychiatric comorbidities are common among people with specific phobias.[12]
- *SAD (or social phobia):* Youth with SAD worry about the perceptions of peers in social settings.[12,160] Usually, this disorder presents in early adolescence (late school age)[160] with median age of onset of 13 years in the US.[12] Psychiatric comorbidities including other anxiety disorders are common.[12]
- *Panic disorder*: Youth with panic disorder experience panic attacks. Notably, panic attacks can occur as a symptom of other psychiatric conditions, without meeting criteria for the diagnosis of panic

disorder.[12] Panic disorder usually presents during adolescence in youth (median age of onset is 20-24 years in the US[12]).[160] Panic disorder rarely occurs in children[12] and is unlikely to manifest in preschool-aged children.[27] Psychiatric comorbidities are relatively common, with an estimated 80% of people with the disorder also being diagnosed with another mental health disorder in their lifetime.[12]

- *Agoraphobia*: Youth with agoraphobia worry about the inability to escape from situations or enclosed spaces.[12,160] If it occurs in youth, this disorder usually presents during later adolescence (mean age of onset is 21 years).[12,160] This disorder is usually chronic and highly comorbid with at least one other mental health diagnosis, most commonly including another anxiety disorder, depressive disorder, PTSD, or alcohol use disorder.[12]
- *GAD:* Youth with GAD worry about multiple things that may occur during normal daily activities.[12,160] This disorder is relatively less common in youth, as it has a mean age of onset of 35 years in the US. Approximately 1% of adolescents are diagnosed with GAD within a 12-month period; onset of the disorder at an earlier age is associated with greater severity and impairment. Depressive and anxiety disorder comorbidities are common.[12]

In total, we reviewed 7 recent pediatric anxiety disorders treatment guideline or guidance statements for information about the key research questions of this report: 1) the place-in-therapy of antidepressants; 2) recommended pediatric age(s) for starting antidepressant therapy; and c) recommendations for using ≥ 2 antidepressants simultaneously for the same condition in the pediatric population (multiple antidepressant therapy). Information about the key questions in the setting of anxiety disorders are summarized in the following sections. Refer to **Table 3** for information from recent guidelines or guidance statements on the management of anxiety disorders, with a focus on key questions 2 and 3.

6.3.1 Key Question 1: Guideline/Guidance Place-in-Therapy of Antidepressants for Pediatric Anxiety Disorders

Treatment of anxiety disorders may depend on severity, and is guided by treatment response, and sometimes, age. Treatment options include psychoeducation and other psychosocial interventions, psychotherapy (primarily with CBT), and medications.[16,31,163,164] Regardless of the type of anxiety, treatment options are similar, although the level of evidence for a particular treatment may vary by anxiety disorder.[164] Antidepressants are the primary medication class recommended for pediatric anxiety disorders, with SSRIs often recommended first line.[16,31] Non-SSRI medications/classes considered a treatment option by at least 1 reviewed guideline include benzodiazepines, SNRIs (duloxetine or venlafaxine), buspirone, alpha$_2$ agonists (eg, guanfacine),[16,31] phenelzine (for selective mutism),[164] and clomipramine.[16] However, generally, medications other than SSRIs or SNRIs play a limited role in pediatric anxiety due to limited evidence and/or greater safety concerns.[16,31] For example, alprazolam therapy is conditionally recommended against by the WFBSP (for GAD, separation anxiety or mixed anxiety disorders),[164] and benzodiazepines are not recommended as part of first-line monotherapy or for long-term therapy by Florida guidance.[16]

Initial therapy for anxiety disorders may be psychoeducation, CBT, and/or medications. Some guidelines or expert guidance recommend psychoeducation and CBT as initial therapy for mild to moderate presentations[16,163] or in general,[165] while medications are suggested after an insufficient response CBT

therapy or for higher severity cases.[16,163] Unlike other guidelines, RANZCP (2018) recommends that an expert should be consulted before starting medications.[165] Due to insufficient evidence to prioritize treatments over others (ie, CBT before SSRI therapy), the AACAP (2020) does not provide formal recommendations for which treatment should be first line overall.[17] Nonetheless, the AACAP informally recognizes that CBT may be prioritized over medications for lower severity cases, while for higher severity cases or when access to CBT is lacking, medications may be prioritized. Formal recommendations by the AACAP are to offer CBT, SSRIs, or SNRIs (except atomoxetine) to youth ages 6-18 with SAD, GAD, separation anxiety or panic disorder; recommendations for CBT or SSRI are rated higher (level 1) than SNRI therapy (level 2), denoting greater certainty that the benefits of CBT and SSRIs outweigh risks. The AACAP also formally recommends the option to prioritize combination therapy with CBT and SSRI over CBT or SSRI monotherapy (at level 2) since some evidence suggests combination therapy may be more beneficial in the short term.[17]

Regarding recommendations for specific SSRIs or SNRIs, the level of evidence for treating anxiety disorders in children and adolescents varies by medication and guideline. Guidelines mentioning specific SNRIs each recognize duloxetine and venlafaxine as agents with demonstrated efficacy (in at least 1 RCT[164]) for pediatric anxiety.[16,17,31,163,164] SSRIs recognized as being efficacious (in at least 1 RCT[164]) for treatment of an anxiety disorder among children and adolescents by guidelines mentioning specific SSRIs are fluoxetine, sertraline, and fluvoxamine.[16,17,31,163,164] Escitalopram, citalopram, and paroxetine are recognized treatment options by 3 of 5 guidelines, generally for later-line therapy due to lower levels of evidence for pediatric anxiety.[16,17,31,163,164] The WFBSP (2023) opted to rate the level of evidence for treatment options for several anxiety disorders separately (see Table 3).[164]

Some antidepressant classes or specific antidepressants are **not** considered as treatment options by one or more reviewed guidelines:

- There is a lack of controlled trials using TCAs to treat anxiety disorders among youth in general.[31] Florida guidance recommends against TCAs for children under 6 years old.[16]
- While several guidelines including AACAP consider the SSRI paroxetine as a treatment option like other SSRIs, [17,31,164] Canadian guidance recommends avoiding paroxetine due to a possibly higher incidence of withdrawal side effects.[163] Florida guidance also considers paroxetine as a later-line pharmacotherapy option (third line or later) after trials of other SSRIs and SNRIs due to its safety profile.[16] Among other safety or tolerability concerns, paroxetine use is associated with increased suicidality in youth relative to other SSRIs.[16,17]

There is insufficient evidence to guide the optimal duration of pharmacotherapy; the AACAP recommends treating for about 12 months following symptom remission, with consideration to longer for increased complexity or severity.[17]

Most guidelines provide little guidance about the approach to therapy after initial treatment failure. Generally, if first-line pharmacotherapy with an SSRI fails, guidelines suggest switching to another SSRI or an SNRI, or combination therapy with CBT.[16,17,31] Canadian expert guidance considers combination psychotherapy and medication therapy an option after a partial response to psychotherapy.[163] Maudsley expert guidance also lists the option of changing medications (to another SSRI or other agent), combining medications to manage comorbidities, or possibly augmentation of SSRI therapy with other medications.[31] Florida guidance is the most specific, recommending combination SSRI+CBT (second line),

switching to another SSRI with CBT (third line), or switching to an SNRI (fourth line) for youth ages 6-17.[16]

Notably, reviewed clinical practice guidelines used different approaches to making treatment recommendations. Several guidelines provide recommendations for treatment anxiety disorders as a group (ie, Canadian Pediatric Society [2023], Florida guidance [2022], and Maudsley expert guidance [2021]),[16,31,163] whereas others make recommendations or evaluations specific to one or more disorders. Formal recommendations by the 2020 AACAP guideline are specific to treatment of SAD, GAD, separation anxiety, or panic disorder in youth.[17] The WFSBP (2023) graded evidence levels for treatments of GAD, SAD, selective mutism, and mixed anxiety disorders (GAD, SAD, and/or separation anxiety).[164] Finally, the RANZCP (2018) makes formal recommendations for anxiety disorders in general, except for separation anxiety disorder.[165]

6.3.2 Key Question 2: Guideline or Expert Guidance Recommendations for Age to Receive an Antidepressant for Anxiety Disorders

Unlike US pediatric anxiety treatment guidelines from the Florida group and AACAP,[16,17] 5 reviewed international guidelines or expert guidance statements do not specify ages for initiating pharmacotherapy in youth with an anxiety disorder.[31,138,163-165]

Both reviewed US guidelines (Florida and AACAP) consider SSRIs or SNRIs as options for treating anxiety disorders in children or adolescents aged 6 or older.[16,17] While Florida guidance addresses treatment of any anxiety disorder in general,[16] recommendations to treat children ages 6 or older from the AACAP are specific to treating SAD, GAD, separation anxiety, or panic disorder.[17] The AACAP considers SSRIs or SNRIs as treatment options for children as young as 6 years old, but pointed out that available evidence is most applicable to children and adolescents ages 8 to 18 years old.[17] The minimum age of 6 years per US guidelines is mostly consistent with the minimum age of children included by at least 1 RCT per drug class (SSRI or SNRI), according to evidence cited by the 2023 WFSBP guideline.[164] One exception is sertraline, which has been studied in children with an anxiety disorder as young as 5 years.[166] See Table 3 for age ranges of children and adolescents included in RCTs studying SSRIs or SNRI for anxiety disorders per the WFSBP.

Florida and Maudsley prescribing guidance also address pharmacotherapy in younger children (eg, preschool age[31] or under 6 years[16]) with an anxiety disorder. Evidence for using SSRIs in children under 6 years old is limited, so additional caution is recommended when considering pharmacotherapy for this age group.[16,27] Fluoxetine is a treatment option for preschool-aged children who fail psychosocial treatments (or 4 to <6 years per Florida guidance).[16,31] Sertraline is also an option after failure of fluoxetine for children ages 4 to under 6 years according to Florida guidance, [16] with both fluoxetine and sertraline only recommended for use in combination with psychosocial treatments.[16] The recommendations from Florida and Maudsley guidance align closely with those presented in the guideline specifically addressing the treatment of preschool-aged children are by Gleason et al (2007). According to Gleason and colleagues, based on evidence from case reports or expert opinion, fluoxetine or fluvoxamine (after failure of fluoxetine) are options for preschool-aged children with certain anxiety disorders (separation anxiety, GAD, selective mutism, or specific phobia) and significant functional impairment despite psychotherapy.[27]

6.3.3 Key Question 3: Guideline or Review Guidance about Multiple Antidepressant Therapy for Anxiety Disorders

Of 7 recent (2018-2023) clinical practice guidelines or expert guidance statements for the treatment of pediatric anxiety disorders, only the US Florida expert guidance (2022) specifically mentions the option for MAT. According to the Florida guidance, based on limited evidence, MAT with an SSRI or SNRI and the TCA, clomipramine, may be an option for youth 6-17 years old with a partial response to SSRI and SNRI monotherapy. Clomipramine is one of several options that Florida guidance lists as options for monotherapy or augmentation of SSRI/SNRI therapy (alternatives are buspirone, alpha$_2$-agonists, or low-dose benzodiazepines).[16]

Other guidelines suggest there is a paucity of data for combination pharmacotherapy (with antidepressants or other agents) in youth for the treatment of anxiety disorders.[16,17,165] Even for treatment-resistant cases, the RANZCP guideline states that combination pharmacotherapy in general should be avoided among people with anxiety (no specific age mentioned) due to a lack of evidence for benefit.[165]

Similar to antidepressants used for depression, combination therapy with strong serotonergic agents should be avoided. The combination of an SSRI or SNRI and MAOI is contraindicated.[17]

Table 3. Pediatric Anxiety Disorders Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
Canadian Pediatric Society (CPS) Position Statement; 2023[163] *Target pediatric population(s): Children and youth* ***(specific ages not defined).***	
• **Pharmacotherapy is an option after first-line psychotherapy for *children* and *adolescents* with mild-moderate anxiety**, or as **part of first-line therapy for moderate or acute symptoms**. Combined treatment with psychotherapy is an option for children also. ○ SSRI options for anxiety disorders in general: citalopram, escitalopram, fluvoxamine, sertraline, fluoxetine ○ SNRI options for social anxiety, generalized anxiety, separation anxiety or panic disorder: venlafaxine, duloxetine • The following information is provided about age for pharmacotherapy treatment: ○ Developmental age/stage should be considered when prescribing medication	• **No information provided about combination therapy with antidepressants.** • The combination of an SSRI and CBT is an initial treatment option for moderate to severe anxiety disorders.
World Federation of Societies of Biological Psychiatry (WFSBP)–Part 1. Anxiety Disorders; 2023[164] *Target pediatric population(s): Children and adolescents* ***(specific ages not defined)[b]***	
• **No specific age(s) provided for initiation of antidepressants**. The min/max age range of children and/or adolescents in RCTs cited for treatment of 1 or more anxiety disorders with an antidepressant per drug is as follows: ○ SSRIs: fluvoxamine: 6-17 years[167]; sertraline: 5-17 years[166,168]; escitalopram: adolescents (mean 14.8 years)[169]; fluoxetine: 7-17 years[170,171]; paroxetine: 8-17 years[172] ○ SNRIs: duloxetine: 7-17 years[173]; venlafaxine ER: 6-17 years[174,175] • *Child and adolescent* recommended antidepressant options by target disorder(s)[a]: ○ GAD/SAD/mixed multiple-anxiety disorders: ▪ SSRIs: Fluvoxamine (1A), sertraline (1A), escitalopram (2B), fluoxetine (2B) ▪ SNRIs: Duloxetine (2B), venlafaxine (2B) ○ SAD alone: ▪ SSRIs: paroxetine (2B), fluoxetine (3B – fluoxetine was less effective than CBT); SNRI: venlafaxine (2B) ○ Selective mutism: ▪ SSRIs (citalopram, escitalopram, fluoxetine, sertraline), or the MAOI, phenelzine (each 3C)	• **No combination antidepressant options provided.** For adults, only medications combinations with non-antidepressants (eg, benzodiazepines) were provided as options. • For mixed anxiety disorders (GAD, SAD, separation anxiety, other) in children/adolescents, CBT with sertraline was superior to sertraline alone in 1 RCT (2B)

[a] AACP formal recommendations: strength: 1= benefits clearly outweigh the risks, and 2= there is uncertainty about whether the benefits outweigh the risks; evidence from a high-quality SR: B = most outcomes from RCTs or observational studies were of moderate quality; C = most outcomes from RCTs or observational studies were of low quality

WFSBP formal recommendations: Strength of recommendation: 1 = strong for; 2 = limited for; 3 = weak for; LOE: A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trials; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias.

Florida Best Practice Guideline recommendations: Recommendations are from consensus of an expert panel who considered the best available evidence (ie, RCTs or SRs prioritized if available) and expert opinion. Recommendations are prioritized by the strength of available recommendations; recommendations range between level 1 (strongest evidence) up to level 7 (weakest evidence). Some treatments are also "Not Recommended," though the strength of evidence for recommending against is not specified.

RANZCP: EBR, indicates there was sufficient evidence to make a recommendation. LOE: I, evidence is from systematic reviews of randomized controlled trials

[b] The WFSBP does not always differentiate medication options for adults from children/adolescents. Only medication options specifically listed for children and/or adolescents are provided.

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CPS, Canadian Pediatric Society; DSM, Diagnostic and Statistical Manual of Mental Disorders; EBR, evidence-based recommendation; ER, extended release; GAD, generalized anxiety disorder; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT, randomized controlled trial; SAD, social anxiety disorder; SNRI(s), serotonin and norepinephrine reuptake inhibitors; SR(s), systematic review(s); SSRI(s), selective serotonin reuptake inhibitor(s); TCA(s), tricyclic antidepressant(s); WFSBP, World Federation of Societies of Biological Psychiatry

Table 3. Pediatric Anxiety Disorders Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents–Anxiety Disorders section; 2022[16] *Target pediatric population(s): Children and adolescents with an anxiety disorder (no specific target disorder is mentioned). Treatment recommendations provided for age <6 years and ages 6-17 years.*	

• Antidepressant options **for children <4 years old:**
  ○ No antidepressant-specific options provided. Generally, medications (monotherapy at the lowest possible dose is preferred) should only be used after an insufficient response to psychosocial therapies once the diagnosis is confirmed and the potential benefits are considered to outweigh the risks (level 2 for all mental health conditions).
• Antidepressant options **for children 4 to <6 years old.** "The data for treating anxiety disorders with psychopharmacologic medication in young children is limited. Thus, exercise caution in prescribing pharmacological treatment below age 6" (page 32):
  ○ Fluoxetine in combination with psychotherapy is an option (level 2) for **children 4-5 years old** with an unsatisfactory response to 12 weeks of psychosocial therapies (parental management and CBT)
  ○ Sertraline in combination with psychotherapy may be considered (level 3) after failure of an adequate fluoxetine trial
• Antidepressant options **for children 6-17 years:**
  ○ Fluoxetine or sertraline as monotherapy or in combination with psychotherapy are options (level 2a) for treatment of moderate to severe anxiety symptoms or for mild to moderate anxiety that insufficiently responded to evidence-based psychosocial interventions.
  ○ Additional options after failure of sertraline and fluoxetine in the preferred trial order: duloxetine ± CBT (level 3a); escitalopram ± CBT, specifically **for ages 12-17** (level 3b); fluvoxamine ± CBT (level 3c)
  ○ Additional options after failure of level 3 options and confirmation of the diagnosis: citalopram with CBT or venlafaxine with CBT (level 4)
  ○ Other antidepressant options (no level, "limited evidence"): clomipramine (among other options)
• Antidepressants **NOT recommended for age <6 years**: TCAs
• Antidepressants **NOT recommended for age 6-17 years**: paroxetine as a first- or second-line option
	• For youth 6-17 years old, **augmentation of an SSRI or SNRI with clomipramine** is an option if the patients have an insufficient response to recommended SSRI and SNRI monotherapy (no assigned level; based on "limited evidence")
	• Cross-titration between antidepressants is the recommended strategy for switching between agents, if tolerated

British Association of Psychopharmacology (BAP)–Expert Opinion Response to Common Practical Questions; 2022[138] *Target pediatric population(s): Children and adolescents* ***(specific ages not defined).***	
• No specific information provided about target ages	• No information provided on combination antidepressant use

[a] AACP formal recommendations: strength: 1= benefits clearly outweigh the risks, and 2= there is uncertainty about whether the benefits outweigh the risks; evidence from a high-quality SR: B = most outcomes from RCTs or observational studies were of moderate quality; C = most outcomes from RCTs or observational studies were of low quality

WFSBP formal recommendations: Strength of recommendation: 1 = strong for; 2 = limited for; 3 = weak for; LOE: A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trials; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias.

Florida Best Practice Guideline recommendations: Recommendations are from consensus of an expert panel who considered the best available evidence (ie, RCTs or SRs prioritized if available) and expert opinion. Recommendations are prioritized by the strength of available recommendations; recommendations range between level 1 (strongest evidence) up to level 7 (weakest evidence). Some treatments are also "Not Recommended," though the strength of evidence for recommending against is not specified.

RANZCP: EBR, indicates there was sufficient evidence to make a recommendation. LOE: I, evidence is from systematic reviews of randomized controlled trials

[b] The WFSBP does not always differentiate medication options for adults from children/adolescents. Only medication options specifically listed for children and/or adolescents are provided.

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CPS, Canadian Pediatric Society; DSM, Diagnostic and Statistical Manual of Mental Disorders; EBR, evidence-based recommendation; ER, extended release; GAD, generalized anxiety disorder; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT, randomized controlled trial; SAD, social anxiety disorder; SNRI(s), serotonin and norepinephrine reuptake inhibitors; SR(s), systematic review(s); SSRI(s), selective serotonin reuptake inhibitor(s); TCA(s), tricyclic antidepressant(s); WFSBP, World Federation of Societies of Biological Psychiatry

Table 3. Pediatric Anxiety Disorders Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])
The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition – Ch. 5 Children and Adolescents; 2021[31] *Target pediatric population(s): Children and adolescents **(specific age range not defined)** with anxiety disorders.*	
• SSRIs are a preferred first-line option when pharmacotherapy is indicated; there is RCT evidence for using sertraline, fluoxetine, fluvoxamine, and paroxetine in children/adolescents. SNRIs are suggested as a third-line option after failure of 2 different SSRIs due to tolerability issues; there is at least 1 RCT of venlafaxine and duloxetine in children/adolescents. • There is a **lack of controlled clinical trials to support TCA use in children.** • **In pre-school aged children, there is a lack of clinical trial evidence for pharmacotherapies**. However, if psychotherapy fails or when symptoms are severe and ongoing**, fluoxetine** (or buspirone) **may be options based on case report evidence**.	• **No information provided about combined antidepressants in children or adolescents.** • Combining an antidepressant with CBT, switching medications, or "…combining medications (e.g., for co-morbidities, to treat side effects, to potentiate action)" (page 559) are suggested options for poor treatment response. There is a lack of evidence for other augmentation strategies (eg, adding buspirone).
American Academy of Child and Adolescent Psychiatry (AACAP); 2020[17] *Target pediatric population(s): Children or adolescents with an anxiety disorder.* *Medication treatment recommendations were not provided for specific phobia disorders or selective mutism since the sources of evidence did not address treatment of these disorders.*	
• Pharmacologic and non-pharmacologic treatment evidence (per a 2017 SR including RCT or observational study evidence) for various anxiety disorders was considered **most applicable to children and adolescents 8-18 years old, on average. Medication and therapy studies included children as young as 6 years old.** Though, very young children were not well-represented in studies. • **SSRIs are an option for *children* and *adolescents 6-18 years old*** with SAD, GAD, separation anxiety, or panic disorder **(1B)** ○ Specific SSRIs with "sufficient" evidence: fluoxetine, fluvoxamine, paroxetine, sertraline; though guideline authors expect SSRIs as a class to offer similar benefits • **SNRIs are an option for *children and adolescents 6-18 years old*** with SAD, GAD, separation anxiety, or panic disorder **(2C)** ○ Specific SNRIs with "sufficient" evidence: duloxetine and venlafaxine; though guideline authors expect SNRIs (except atomoxetine) as a class to offer similar benefits	• **No long-term combination or augmentation medication treatment options provided** ○ Cross-tapering is a short-term option to switch between SSRIs • CBT with an SSRI (for ages 6-18 years) may be preferred to CBT or SSRIs alone (2C) for treatment of SAD, GAD, separation anxiety or panic disorder • MAOIs should <u>not</u> be combined with another serotonergic drug to avoid serotonin syndrome, the combination of an MAOI and SSRI or SNRI is <u>contraindicated</u>. Non-MAOI serotonergic drugs (including SSRIs, SNRIs, and others) should be combined <u>cautiously</u> (eg, starting the second agent at a very low dose with slow up-titration of dose) to avoid serotonin syndrome.

[a] *AACP formal recommendations: <u>strength:</u> 1= benefits clearly outweigh the risks, and 2= there is uncertainty about whether the benefits outweigh the risks; <u>evidence from a high-quality SR</u>: B = most outcomes from RCTs or observational studies were of moderate quality; C = most outcomes from RCTs or observational studies were of low quality*

WFSBP formal recommendations: <u>Strength of recommendation:</u> 1 = strong for; 2 = limited for; 3 = weak for; <u>LOE:</u> A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trials; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias.

Florida Best Practice Guideline recommendations: Recommendations are from consensus of an expert panel who considered the best available evidence (ie, RCTs or SRs prioritized if available) and expert opinion. Recommendations are prioritized by the strength of available recommendations; recommendations range between level 1 (strongest evidence) up to level 7 (weakest evidence). Some treatments are also "Not Recommended," though the strength of evidence for recommending against is not specified.

RANZCP: EBR, indicates there was sufficient evidence to make a recommendation. <u>LOE:</u> I, evidence is from systematic reviews of randomized controlled trials

[b] *The WFSBP does not always differentiate medication options for adults from children/adolescents. Only medication options specifically listed for children and/or adolescents are provided.*

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CPS, Canadian Pediatric Society; DSM, Diagnostic and Statistical Manual of Mental Disorders; EBR, evidence-based recommendation; ER, extended release; GAD, generalized anxiety disorder; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT, randomized controlled trial; SAD, social anxiety disorder; SNRI(s), serotonin and norepinephrine reuptake inhibitors; SR(s), systematic review(s); SSRI(s), selective serotonin reuptake inhibitor(s); TCA(s), tricyclic antidepressant(s); WFSBP, World Federation of Societies of Biological Psychiatry

Table 3. Pediatric Anxiety Disorders Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	**Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])**
Royal Australian and New Zealand College of Psychiatrists (RANZCP); 2018[165] *Target pediatric population(s): Children and adolescents **(no exact age specified**) with an anxiety disorder except separation anxiety (this is not addressed by the guideline).* *Of note, this guideline primarily focuses on adults, providing very few and less specific recommendations for youth.*	
• **No specific age recommendations given for antidepressant therapy.** It is advised to consult with a specialist before prescribing medications for anxiety disorders in youth (EBR). The recommended first-line treatment is CBT, adapted to the age of the child/adolescent (EBR, LOE I).	• In the context of treatment-resistant cases, it is stated that "Combination pharmacotherapy or augmentation should be avoided" (page 1152) and there is little evidence to support that combination therapy is beneficial. The target age group for this recommendation is not specified.

[a] AACP formal recommendations: strength: 1= benefits clearly outweigh the risks, and 2= there is uncertainty about whether the benefits outweigh the risks; evidence from a high-quality SR: B = most outcomes from RCTs or observational studies were of moderate quality; C = most outcomes from RCTs or observational studies were of low quality

WFSBP formal recommendations: Strength of recommendation: 1 = strong for; 2 = limited for; 3 = weak for; LOE: A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trials; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias.

Florida Best Practice Guideline recommendations: Recommendations are from consensus of an expert panel who considered the best available evidence (ie, RCTs or SRs prioritized if available) and expert opinion. Recommendations are prioritized by the strength of available recommendations; recommendations range between level 1 (strongest evidence) up to level 7 (weakest evidence). Some treatments are also "Not Recommended," though the strength of evidence for recommending against is not specified.

RANZCP: EBR, indicates there was sufficient evidence to make a recommendation. LOE: I, evidence is from systematic reviews of randomized controlled trials

[b] The WFSBP does not always differentiate medication options for adults from children/adolescents. Only medication options specifically listed for children and/or adolescents are provided.

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association of Psychopharmacology; CBT, cognitive behavioral therapy; CPS, Canadian Pediatric Society; DSM, Diagnostic and Statistical Manual of Mental Disorders; EBR, evidence-based recommendation; ER, extended release; GAD, generalized anxiety disorder; LOE, level of evidence; MAOI(s), monoamine oxidase inhibitor(s); RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCT, randomized controlled trial; SAD, social anxiety disorder; SNRI(s), serotonin and norepinephrine reuptake inhibitors; SR(s), systematic review(s); SSRI(s), selective serotonin reuptake inhibitor(s); TCA(s), tricyclic antidepressant(s); WFSBP, World Federation of Societies of Biological Psychiatry

6.4 Obsessive-Compulsive Disorder (OCD)

OCD is characterized by excessive and distressing intrusive thoughts, images, or sensations (obsessions) and ritualized or repetitive behaviors (compulsions) that are often driven by the obsessions.[9,176] Examples of obsessive thoughts include the fear of contamination or intrusive religious fears, and examples of compulsions are excessive hand washing or ritualized counting.[9] Although symptoms of OCD overlap with some anxiety disorders, OCD and related disorders are considered distinct from anxiety disorders.[176] Other disorders considered to be related to OCD by the DSM-5-TR include body dysmorphic disorder, hoarding disorder, trichotillomania, and excoriation disorder, among others.[176] Without treatment, OCD is usually a chronic disorder; however, OCD symptoms may remit by early adulthood among many individuals with onset before adulthood.[176]

Each year approximately 1% of the US population suffers from OCD. Mean age of onset of OCD in the US is in young adulthood and diagnosis after age 35 is rare. Yet, up to a quarter of cases present by age 14 and the peak onset age is earlier among men.[176] Mean age of diagnosis among people with pediatric OCD is approximately 10 years old,[44] and onset during pre-school age is possible, although rare.[27] Mental health comorbidity is very common among youth with OCD, with up to 85% of youth with OCD affected by at least one other condition.[86] Anxiety disorders and Tic disorders (especially among young male youth[176]) are common co-occurring conditions.[176]

In total, we reviewed 7 recent pediatric OCD treatment guideline or guidance statements for information about the key research questions of this report: 1) the place-in-therapy of antidepressants; 2) recommended pediatric age(s) for starting antidepressant therapy; and c) recommendations for using ≥ 2 antidepressants simultaneously for the same condition in the pediatric population (multiple antidepressant therapy). Information about the key questions in the setting of OCD are summarized in the following sections. Refer to **Table 4** for information from recent guidelines or guidance statements on the management of OCD, with a focus on key questions 2 and 3. Note that all reviewed guidelines for the treatment of pediatric OCD focus on treatment of OCD specifically, except for the 2019 Indian Psychiatric Society guideline and 2021 Maudsley prescribing guideline which also address body dysmorphic disorder.[31,177]

6.4.1 Key Question 1: Guideline/Guidance Place-in-Therapy of Antidepressants for Pediatric Anxiety Disorders

Treatment options for pediatric OCD include CBT and medications, with specific SSRIs as first-line pharmacotherapy options. Generally, CBT is recommended as a first-line treatment option in general or for mild-moderate pediatric OCD specifically,[16,44,86] and the combination of CBT and SSRI therapy is recommended for moderate-severe pediatric OCD.[16,44,177] The SSRIs fluvoxamine, fluoxetine, and sertraline have been proven effective for pediatric OCD, and are specifically recommended as first-line options by several guidelines.[16,86,178] Clomipramine, a TCA and non-selective serotonin reuptake inhibitor (NSSRI), is also effective for treatment of pediatric OCD; however, it is usually not recommended first line due to an inferior safety profile to SSRIs.[16,44,86,178] For treatment of OCD with an SSRI, moderate-to-high doses (eg, fluoxetine 60 mg in an adolescent) are usually needed. Compared to other indications for

SSRIs, OCD symptoms may take longer to respond; a full 10-12-week trial of high-dose SSRI is recommended by experts.[16,44,138]

Partial response to treatment is common among youth with OCD,[16,44] and true treatment-resistant OCD (ie, failure of an adequate trial of 2 serotonin reuptake inhibitors [ie, SSRI or clomipramine] and CBT) may occur in about 10% of pediatric cases.[177] Notably, the risk of suicide in youth with OCD taking antidepressants is considered smaller than the risk of adolescents with depression[31,44]; in one pooled analysis of pediatric OCD trials, the absolute risk of suicide with SSRIs was small and not significantly greater than placebo.[44] Medications should continue for at least 6-12 months after initial symptomatic improvement,[44,86] but longer durations of treatment (eg, years) may be needed for youth who relapse after medication cessation.[44]

6.4.2 Key Question 2: Guideline or Expert Guidance Recommendations for Age to Receive an Antidepressant for OCD

Of the 6 reviewed guidelines (see Table 4), the Florida and Maudsley guidance statements were the only ones that provided specific guidance about target ages for antidepressant use. The Florida guidance (2022) treatment algorithm considers medications, primarily select SSRIs or clomipramine, as options for youth between 6-17 years old.[16] Of the first-line SSRIs recommended by Florida guidance (ie, sertraline, fluoxetine, or fluvoxamine), sertraline is recommended for the youngest age of 6 or older.[16] Most recommendations by the Maudsley prescribing guideline (2021) for pediatric OCD are not specific to age; however, drawing from a NICE guideline, Maudsley assigned a stronger recommendation for using combination CBT and SSRI therapy for youth ages 12-18 years old (*offer* treatment after failure of monotherapy) than youth ages 8-11 years old (*consider* combination therapy).[31]

Despite not targeting a particular age range for general treatment recommendations, several guidelines included information to determine the studied age range of an antidepressant in pediatric OCD clinical trials or stated the minimum age for use of an antidepressant based on an antidepressant's regulatory agency approval. Specific target ages mentioned per antidepressant are as follows:

- Sertraline: Age ≥ 6 years[16,31,177] (studied in ages 6-17 years[178])
- Fluoxetine: Age ≥ 7 years[16] or ≥ 8 years[177] (studied in ages 8-17 years[178])
- Fluvoxamine: Age ≥ 8 years[16,31,177] (studied in ages 7-17 years[178]); recommended to use a lower dose for children 6-11 versus 12-17[86]
- Paroxetine: Age ≥ 8 years[177] (studied in ages 7-17 years[178]). Other guidelines do not recommend paroxetine[31] or did not provide a recommendation due to inconsistent evidence.[178]
- Citalopram: Studied in ages 7-18 years. One guideline considered citalopram evidence for OCD to be insufficient.[178]
- Escitalopram: Second-line SSRI option, with target age or studied ages not specified.[16]
- Clomipramine: Age ≥ 5[177] or ≥ 10 years[16] (studied in ages 6-18 years)[178]

According to the 2007 guideline by Gleason et al addressing psychiatric pharmacotherapy for pre-school aged children, low-dose SSRIs (fluoxetine, fluvoxamine, or sertraline) can be considered in combination with psychological/behavioral therapy for very young children with OCD and significant functional impairment who fail evidence-based psychosocial therapy. However, evidence for using

pharmacotherapy in pre-school aged children with OCD is very limited. At the time of the 2007 guideline, no empirical studies of pharmacotherapy for pre-school age OCD were available, and evidence for using an SSRI was limited to case reports of fluoxetine to treat anxiety disorders in children 2.5-4 years old.[27]

The safety profile of antidepressants may differ in youth compared to adults and can vary depending on the youth's age. According to the International Accreditation Task Force (IATF) for OCD (2021), side effects of SSRIs are more frequent in youth under 12 years old compared to adults.[86] Behavioral side effects may be frequent in younger children treated with antidepressants.[44]

6.4.3 Key Question 3: Guideline or Review Guidance about Multiple Antidepressant Therapy for OCD

Four of 6 reviewed guidelines (see Table 4) consider **augmentation of SSRI therapy with clomipramine** to be an option for difficult-to-treat or treatment-resistant pediatric OCD. The Indian Psychiatric Society (2019) recommends a trial of clomipramine augmentation before an antipsychotic[177]; however, experts from BAP consider antipsychotic augmentation to be a more common treatment strategy for pediatric treatment-resistant OCD.[138] According to the OCD IATF, evidence for augmentation of an SSRI with a low-dose antipsychotic is primarily extrapolated from adults, and the treatment approach may be particularly useful for youth with a comorbid tic disorder.[86] Evidence for combination therapy with an SSRI and clomipramine in youth is supported by expert opinion and 2 small case series (see more details on this in section 6.4.3.1 below).[86]

Regarding augmentation of SSRI therapy with clomipramine, combination therapy with certain SSRIs may be more advantageous than others. Combining clomipramine with an SSRI is thought to boost overall serotonergic effects, while potentially minimizing adverse effects of each individual drug.[44] Clomipramine metabolism is inhibited by fluvoxamine (by weak inhibition of CYP450 1A2, 2C19, and 3A4[179]) creating pharmacokinetic synergy[44,177]: the inhibition prevents clomipramine conversion to des-methyl-clomipramine increasing the serum levels of clomipramine.[44] Preventing clomipramine conversion to des-methyl-clomipramine may also minimize treatment-limiting adrenergic side effects.[179] In contrast, extra caution is advised when combining clomipramine with SSRIs that strongly inhibit CYP450 2D6 (fluoxetine or paroxetine)[44,177] because this pharmacokinetic interaction may boost des-methyl-clomipramine, increasing harmful side effects.[179] Regardless of which SSRI is used with clomipramine, close monitoring for adverse effects, especially serotonin syndrome[179] and cardiotoxicity from clomipramine (with EKG monitoring)[44] is recommended. Therapeutic drug-level monitoring of clomipramine levels may be considered.[44]

6.4.3.1 Other References to MAT by Expert Opinion Reviews

No systematic reviews were identified from a supplemental literature search for reviews addressing MAT for pediatric OCD. Only one review (Diaz-Caneja et al 2014[34]) focused specifically on pediatric polypharmacy with antidepressants, however, this review is non-systematic[‡‡]. Evidence summarized

[‡‡] We considered Diaz-Canaja and colleagues (2014) to be non-systematic due to only searching one bibliographic database and not evaluating the quality of the reviewed evidence. Their literature search for pediatric polypharmacy primary studies extended through 2012.

below is from non-systematic reviews, which incidentally mentioned MAT. Reviewed pediatric evidence for MAT is limited to observational or descriptive data.

- **Clomipramine:** Augmentation of SSRI therapy with clomipramine for treatment-resistant pediatric OCD is also mentioned by several older (2005-2015) expert opinion review articles.[34,180-182] The level of evidence supporting combination therapy with an SSRI and clomipramine in youth is unclear. There is a lack of clinical trials using this combination in pediatric patients per experts (in 2015).[182] At a minimum, small case series (n=5 and n=4) of pediatric patients (≤ 17 years) support using clomipramine (about 25 to 75 mg daily[§§]) with fluoxetine (20 to 60 mg daily) or sertraline (50 to 200 mg daily), primarily among adolescents (age range 9-17).[183,184] In the case series (n=6) by Simeon et al (1990), patients initiated clomipramine after variable prior treatments (eg, psychotherapy or desipramine) or no treatment (n=2), and fluoxetine was added after insufficient response and/or intolerability to clomipramine.[183] In the second case series by Figueroa et al (1998), clomipramine was added to SSRI therapy (fluoxetine or sertraline) after an insufficient response to 1-2 SSRIs.[184] Combination therapy of clomipramine with an SSRI improved OCD symptoms in most cases, including among patients only with OCD and patients with mood or anxiety comorbidities.[183,184] Tolerability of the SSRI-clomipramine combination varied. Simeon et al considered clomipramine-fluoxetine combination therapy to be better tolerated than clomipramine monotherapy, with mild adverse events of hand tremors, weight loss and sleep disturbances reported; perhaps due to using lower doses of clomipramine when used in combination with fluoxetine.[183] However, Figueroa et al reported cardiac adverse events in 2 of 4 pediatric patients receiving the combination therapy, including QT interval prolongation in both cases and tachycardia in one case. The patient with tachycardia and QT interval prolongation tolerated the combination (sertraline 150 mg + clomipramine dose <100 mg daily) after reducing the clomipramine dose, but QT interval prolongation in the other patient (9-year-old patient taking fluoxetine 40 mg and clomipramine 25 mg daily) led to clomipramine discontinuation.[184] Experts recommending SSRI and clomipramine combination therapy also point to limited clinical evidence in adults. The combination of clomipramine and non-maximal dose SSRI therapy with citalopram or fluoxetine demonstrated benefit in 3 small studies of adults with treatment-resistant or single-SSRI refractory OCD, including a small open-label trial,[185] non-randomized single-arm prospective study,[186] and small open-label RCT.[187] Usually clomipramine was added to SSRI therapy; however, in one of the adult studies, citalopram was added to existing clomipramine therapy.[186]
- **Multiple SSRI, or SSRI and SNRI therapy**: One expert opinion review article (2005) mentioned the option of SSRI+SSRI or SSRI+SNRI therapy as alternatives to clomipramine+SSRI (or other combinations) to boost serotonergic processes in pediatrics with treatment-resistant OCD.[180] However, no evidence was provided to support this practice.

[§§] A higher dose of clomipramine (as high as 100 mg) was used by 1 patient in combination with sertraline (up to 150 mg daily), but this patient developed a prolonged QT interval, resulting in dose-de-escalation of clomipramine to an unknown dose. Most patients in case reports received clomipramine 25-50 mg daily.

Table 4. Pediatric OCD Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, when provided[a])	**Combination Therapy Recommendations (recommendation strength/LOE, when provided[a])**
World Federation of Societies of Biological Psychiatry (WFSBP) – Version 3. Part II. OCD and PTSD; 2023[178] *Target pediatric population(s): Children and adolescents with OCD (but not related disorders such as body dysmorphic disorder)*	
• **No specific age(s) provided for initiation of antidepressants**. The min/max age range of children and/or adolescents based on 1 or more RCTs cited for treatment of OCD[a] with an antidepressant per drug is as follows: ○ SSRIs: Fluvoxamine: 8-17 years[188]; fluoxetine: 6-18 years[189-192]; sertraline: 6-17 years[193-195]; paroxetine: 7-17 years[196]; citalopram: 7-18 years[192] ○ TCAs: clomipramine: 6-18 years[197,198] • **First-line** recommendations medications **for children or adolescents: fluvoxamine, fluoxetine, or sertraline** (1A) • **Clomipramine** is an effective treatment option for children or adolescents (2A) • Select SSRIs have demonstrated inconsistent (paroxetine, D4) or insufficient (citalopram, D4) evidence	• **No combination medication options addressed for children/adolescents** ○ For adults, augmentation of SSRIs with another medication is an option for treatment-resistant OCD, however, none of the recommended combination medication options include another antidepressant • Combination treatment with CBT or ERP and medication is superior to drug treatment alone for children/adolescents (1A)
British Association of Psychopharmacology (BAP)–Expert Opinion Response to Common Practical Questions; 2022[138] *Target population(s): Children and adolescents (specific ages not defined).*	
• No specific information provided about target ages	• **Augmentation of an SSRI with clomipramine** (or alternatively, a low-dose antipsychotic) is a treatment option *for children and young people* after failing 2 trials of high-dose SSRI therapy ○ Augmentation with an antipsychotic rather than clomipramine is 'more common'
Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents–Obsessive Compulsive Disorder section; 2022[16] *Target population(s): Children and adolescents with OCD. Treatment recommendations are provided for ages 6-17 years.*	
• Antidepressant options **for children 6-17 years:** ○ For moderate to severe OCD, **sertraline (age 6+), fluoxetine (age 7+), or fluvoxamine (age 8+)** in combination with behavioral therapy (CBT + EBP) are first-line options (level 1b). ○ For mild to moderate OCD with an insufficient response to CBT of appropriate intensity, monotherapy with sertraline, fluoxetine, or fluvoxamine are options (level 2a) ○ For moderate to severe OCD that fails to respond to recommended first-line SSRI treatment for 10-12 weeks at a target dose, switch to another recommended SSRI (level 2b). ○ For any OCD severity, if prior appropriate 10–12-week SSRI trials failed, switching to another recommended SSRI or **clomipramine (age 10+)** are options (level 3a). **Escitalopram** (no specified age) is also an option (level 3b). ○ If treatment-resistant OCD is confirmed, **clomipramine (10-50 mg/day) augmentation of an SSRI** is an option (level 4)	• **Augmentation of an SSRI with clomipramine** (or alternatively with low-dose aripiprazole) is an option for children and adolescents aged 6-17 years with treatment-resistant OCD

[a] *Based on cited RCTs with age information available in the published abstract or accessible full text*

WFSBP formal recommendations: Strength of recommendation: 1 = strong for; 2 = limited for; 3 = weak for; LOE: A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trial; 4 = no recommendation possible; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias; D = no evidence

IATF: Level of evidence: experts cited the type of evidence supporting the competency/standard including the following among other options: RCT, MA (meta-analysis), TG (treatment guideline), CS (prospective cohort study), CR (case report or case series), and OCT (open-label clinical trial).

AACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes

APA: Formal recommendations were based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

Abbreviations: ASD, autism spectrum disorder; BAP, British Association of Psychopharmacology; BDD, body dysmorphic disorder; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; CR, case report or case series; CS, prospective cohort study; DSM, Diagnostic and Statistical Manual of Mental Disorders; EBP, ?; ER, extended release; ERP, Exposure and Response Prevention therapy; FDA, Food and Drug Administration; IATF, International Accreditation Task Force; LOE, level of evidence; MA, meta-analysis; NICE, National Institute for Health and Care Excellence; OCD, obsessive compulsive disorder; RCT(s), randomized controlled trial(s); SGA, second-generation antipsychotic; SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SSRI(s), selective serotonin reuptake inhibitor(s); TCA(s), tricyclic antidepressant(s); TG, treatment guideline; TRD, treatment-resistant depression; UK, United Kingdom; WFSBP, World Federation of Societies of Biological Psychiatry

The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition – Ch. 5 Children and Adolescents; 2021[31] ***Target pediatric population(s):*** *Children and adolescents (specific age range not defined) with OCD or body dysmorphic disorder (BDD).*	
• Psychological therapies and/or SSRIs are first-line therapies for OCD or BDD. **Sertraline (age 6+) and fluvoxamine (age 8+) are <u>UK-licensed therapies</u> for pediatric OCD**. Fluoxetine is recommended by NICE for treatment of BDD or OCD with co-occurring with depression in youth. "**Paroxetine is not recommended for use in children and young people**" (page 561). ○ According to an algorithm from NICE, **the combination of SSRI + CBT** should be **offered** (after failure of CBT and an SSRI alone) **to youth 12-18 years old** and **may be considered for youth ages 8-11 years old** • Clomipramine is also a treatment option, but it is suggested for use after SSRI therapy. • Less evidence is available for treatment of BDD compared to OCD in children and adolescents.	• **No combination antidepressant treatments** are suggested. • The combination of an SSRI and CBT is a recommended option for most youth with OCD or BDD. • A suggested pharmacologic augmenting strategy for OCD is low-dose risperidone or aripiprazole with an SSRI; generally, this is an option for treatment-resistant cases.
The International Accreditation Task Force (IATF) of the Canadian Institute for Obsessive Compulsive Disorders; 2021[86] *Target pediatric population(s): This expert opinion report includes recommendations in the form of "competencies" and "knowledge standards" for providers treating pediatric OCD. Opinions were formed from published clinical practice guidelines for OCD and recent clinical evidence.*	

• **SSRIs are the recommended first-line pharmacotherapy for OCD in children and adolescents (no specific age range)**, generally recommended after the overall first-line treatment with CBT (RCT, MA, and other review evidence). No specific SSRI is preferred (TG, RCT and MA evidence). After failure of an initial SSRI, consider switching to another SSRI or clomipramine (TG evidence).
  ○ The following agents are specifically listed as treatment options since they are FDA-approved for OCD: sertraline, fluvoxamine, fluoxetine, and clomipramine. Of the SSRIs, sertraline has the best evidence for use. Lower maximal doses of fluvoxamine are suggested for children 6-11 years (200 mg) than 12-17 years (300 mg).
  ○ SNRIs are not recommended due to insufficient evidence.
• **Children <12 years old may be more likely to experience adverse effects** of SSRI therapy than adults, thus SSRIs should be initiated at low doses and titrated slowly. Psychiatric adverse events (eg, activation/impulsivity) are more common in the younger age group.
	• For treatment-resistant (ie, usually failure of at least 2 adequate SSRI treatment trials) or complex cases (ie, when another factor such as comorbidity interferes with optimal OCD treatment outcomes), **augmentation of an SSRI with clomipramine is an option** (TG, CR, and CS evidence).
	  ○ Clomipramine/SSRI dosages should be selected based on the pharmacokinetic properties of the drug and ability to inhibit clomipramine metabolism. Notably, fluvoxamine can inhibit the metabolism of clomipramine.
	• Augmentation of an SSRI with a second-generation antipsychotic (SGA) is also an option for difficult-to-treat cases, primarily based on adult evidence. "SGA augmentation provides best results for children with comorbid tics, also some evidence of comorbid ASD, mood instability, and in refractory OCD (weak evidence)" (page 9) (Other review, RCT and OCT evidence)
	• In cases of OCD polypharmacy when treatment discontinuation is appropriate (eg, sustained symptom remission), experts suggest discontinuing antipsychotics first, followed by clomipramine, and then SSRI therapy.

[a] *Based on cited RCTs with age information available in the published abstract or accessible full text*

WFSBP formal recommendations: <u>Strength of recommendation:</u> 1 = strong for; 2 = limited for; 3 = weak for; <u>LOE:</u> A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trial; 4 = no recommendation possible; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias; D = no evidence

IATF: <u>Level of evidence:</u> experts cited the type of evidence supporting the competency/standard including the following among other options: RCT, MA (meta-analysis), TG (treatment guideline), CS (prospective cohort study), CR (case report or case series), and OCT (open-label clinical trial).

AACP formal recommendations: <u>strength 2</u> = there is uncertainty about whether the benefits outweigh the risks; <u>evidence I</u> = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes

APA: Formal recommendations were based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

Abbreviations: ASD, autism spectrum disorder; BAP, British Association of Psychopharmacology; BDD, body dysmorphic disorder; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; CR, case report or case series; CS, prospective cohort study; DSM, Diagnostic and Statistical Manual of Mental Disorders; EBP, ?; ER, extended release; ERP, Exposure and Response Prevention therapy; FDA, Food and Drug Administration; IATF, International Accreditation Task Force; LOE, level of evidence; MA, meta-analysis; NICE, National Institute for Health and Care Excellence; OCD, obsessive compulsive disorder; RCT(s), randomized controlled trial(s); SGA, second-generation antipsychotic; SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SSRI(s), selective serotonin reuptake inhibitor(s); TCA(s), tricyclic antidepressant(s); TG, treatment guideline; TRD, treatment-resistant depression; UK, United Kingdom; WFSBP, World Federation of Societies of Biological Psychiatry

Indian Psychiatric Society; 2019[177] *Target population(s): Children and adolescents (no age specified) with OCD.*	
• **No specific ages recommended in treatment recommendations:** Select SSRIs (fluoxetine or sertraline before paroxetine or fluvoxamine) are options for monotherapy to treat mild-moderate OCD. These SSRIs should be used with CBT for moderate to severe cases. ○ Minimum ages for antidepressant use per FDA approval are as follows (note that it's unclear, but likely these ages are based on any FDA-approved indication, not OCD specifically): ▪ SSRIs: fluoxetine: 8 years; sertraline: 6 years; fluvoxamine: 8 years; paroxetine: 8 years ▪ Clomipramine: 5 years	• **Augmentation of an SSRI with clomipramine** is an option for children and adolescents (no specified age) with OCD who failed an adequate trial of 2 SSRIs (ie, 12-week trial each at tolerated doses). Augmentation with clomipramine should be tried before augmentation with an antipsychotic. ○ The **combination of fluvoxamine and clomipramine is specifically recommended due to pharmacologic synergy**, although clomipramine with any SSRI is an option ○ **Paroxetine and fluoxetine should be used cautiously with clomipramine** as they can inhibit the metabolism of clomipramine

[a] *Based on cited RCTs with age information available in the published abstract or accessible full text*

WFSBP formal recommendations: Strength of recommendation: 1 = strong for; 2 = limited for; 3 = weak for; LOE: A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trial; 4 = no recommendation possible; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias; D = no evidence

IATF: Level of evidence: experts cited the type of evidence supporting the competency/standard including the following among other options: RCT, MA (meta-analysis), TG (treatment guideline), CS (prospective cohort study), CR (case report or case series), and OCT (open-label clinical trial).

AACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes

APA: Formal recommendations were based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

Abbreviations: ASD, autism spectrum disorder; BAP, British Association of Psychopharmacology; BDD, body dysmorphic disorder; CBT, cognitive behavioral therapy; CCT, controlled clinical trial; CR, case report or case series; CS, prospective cohort study; DSM, Diagnostic and Statistical Manual of Mental Disorders; EBP, ?; ER, extended release; ERP, Exposure and Response Prevention therapy; FDA, Food and Drug Administration; IATF, International Accreditation Task Force; LOE, level of evidence; MA, meta-analysis; NICE, National Institute for Health and Care Excellence; OCD, obsessive compulsive disorder; RCT(s), randomized controlled trial(s); SGA, second-generation antipsychotic; SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SSRI(s), selective serotonin reuptake inhibitor(s); TCA(s), tricyclic antidepressant(s); TG, treatment guideline; TRD, treatment-resistant depression; UK, United Kingdom; WFSBP, World Federation of Societies of Biological Psychiatry

6.5 Post-traumatic Stress Disorder (PTSD)

PTSD can develop in anyone, including children at least 1 year of age, after experiencing or witnessing serious traumatic event(s), such as emotional or physical abuse, accidents, or life-threatening medical emergency. Symptoms of PTSD usually occur within 3 months of the index traumatic event, but sometimes, the spectrum of symptoms necessary for diagnosis manifest years after the event. People with PTSD experience distressing symptoms associated with the event, such as intrusive memories or dreams of the event, desire to avoid places associated with the traumatic event, negative changes in mood and cognition starting or worsening following the event, and increased arousal (eg, irritability or hypervigilance). Very young children (generally less than 6 years old) with PTSD may express symptoms differently, such as through reenacting the trauma during play.[11] Research is limited, but available evidence suggests that PTSD symptoms become chronic in some, but not all young people.[199,200]

Median age of onset of PTSD is young adulthood (age 23).[201] Approximately 2-8% of adolescents are diagnosed with PTSD in their lifetime, with higher rates reported among girls than boys.[11,202] The prevalence of PTSD in younger children is unknown.[202] An estimated 16% of children and adolescents (2 to 18 years old) exposed to a traumatic event will develop PTSD.[203] Mental health comorbidities are common among people with PTSD, with most (about 75%) children or adolescents diagnosed with at least 1 other condition. Trauma-exposed young people are more likely than the general population to develop depression, substance use disorder, and conduct disorder.[31]

In total, we reviewed 6 recent pediatric PTSD treatment guideline or guidance statements for information about the key research questions of this report: 1) the place-in-therapy of antidepressants; 2) recommended pediatric age(s) for starting antidepressant therapy; and c) recommendations for using ≥ 2 antidepressants simultaneously for the same condition in the pediatric population (multiple antidepressant therapy). Information about the key questions in the setting of PTSD are summarized in the following sections. Refer to **Table 5** for information from recent guidelines or guidance statements on the management of pediatric PTSD, with a focus on key questions 2 and 3.

6.5.1 Key Question 1: Guideline/Guidance Place-in-Therapy of Antidepressants for Pediatric Anxiety Disorders

According to recent clinical practice guidelines, the primary recommended treatments for PTSD in youth are psychotherapeutic interventions, including trauma-focused CBT (with the strongest evidence) and eye movement desensitization and reprocessing (EMDR). EMDR is usually recommended after an insufficient response to CBT or if CBT is inaccessible.[16,204,205] Although some SSRIs are FDA-approved for treatment of PTSD in adults,[67,82] evidence to support using SSRIs or other antidepressants to treat PTSD symptoms in children or adolescents is limited. Several recent guidelines (WFSBP, 2023; Australian 2021; International Society for Traumatic Stress Studies, 2019; NICE, 2018) determined there was insufficient evidence to recommend using medications.[204-206] **NICE specifically recommended against offering medications to treat PTSD in youth since the limited evidence does not suggest benefit**.[205] In 2 RCTs evaluating sertraline for pediatric PTSD, sertraline was superior to placebo in only 1 RCT.[178] Nonetheless, Florida guidance (2022) and Australian guidelines (2021), distinguish between treatment with antidepressants for core PTSD symptoms (eg, intrusive memories, avoidance, and/or hypervigilance[207])

and mood dysregulation, depression, or anxiety in people with PTSD.[16,204] **When necessary, Florida guidance recommends fluoxetine or sertraline as later-line options to treat mood symptoms in people with PTSD**.[16]

6.5.2 Key Question 2: Guideline or Expert Guidance Recommendations for Age to Receive an Antidepressant for PTSD

Few reviewed guidelines address details about using antidepressants for pediatric PTSD. According to the Florida best practice guideline (2022), "There is no empirical evidence to support the use of psychotherapeutic medications in children 6 years or younger" (page 61) with PTSD.[16] Fluoxetine or sertraline are later-line options to treat comorbid mood disorders or mood dysregulations, however Florida guidance does not make specific age recommendations when using these medications.[16] According to the WFSBP guideline (20223), sertraline has been studied in RCTs among children 6-17 years old.[178]

Older US guidelines (not formally reviewed for this report), including 2007 guidance (Gleason et al) on treatment of pre-school aged children and a 2010 AACAP guideline addressing PTSD treatment for children and adolescents also address pharmacologic therapy. Due to the lack of evidence in children and availability of evidence to support psychotherapeutic interventions for pre-school aged children, Gleason et al do not recommend any medications for treatment of PTSD, despite indicating that medications are commonly used in clinical practice.[27] Use of TCAs (and benzodiazepines) to treat PTSD in pre-school age children is specifically recommended **against** by Gleason et al.[27] Based on limited empirical evidence (eg, case reports or uncontrolled studies) and/or clinical opinion, the AACAP (2010) stated that SSRIs and non-SSRI medications (eg, antipsychotics, or alpha- or beta-adrenergic blocking agents) may be considered for pediatric PTSD. No specific age recommendations are provided by the AACAP, though described studies included children as young as age 6 (sertraline) or 7 (fluoxetine).[200]

6.5.3 Key Question 3: Guideline or Review Guidance about Multiple Antidepressant Therapy (MAT) for PTSD

None of the 6 reviewed guidelines provided information about MAT for pediatric PTSD. As previously mentioned, there is little evidence to support antidepressant *monotherapy* to treat the core symptoms of pediatric PTSD.[16,178,204] In *adults*, combination treatment with an antipsychotic and SSRI may be an option for treatment-resistant PTSD.[178]

Table 5. Pediatric PTSD Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, if provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, if provided[a])
World Federation of Societies of Biological Psychiatry (WFSBP) – Version 3. Part II. OCD and PTSD; 2023[178] *Target pediatric population(s): Children and adolescents with PTSD*	
• There is little RCT data to guide use of medications to treat PTSD in children/adolescents. Only **sertraline** has been studied, but evidence is inconclusive due to conflicting findings from 2 RCTs (D4). • **No specific age(s) provided for initiation of antidepressants**. The min/max age range of children and/or adolescents based on 1 or more RCTs cited for treatment of PTSD with sertraline: 6-17 years[208,209] • Only CBT is a recommended treatment option (1A) for children/adolescents with PTSD, despite mixed findings in RCTs	• **No information on combined antidepressants provided for children/adolescents** ○ For adults, adjunctive treatment with antipsychotics (olanzapine or risperidone) added to SSRI therapy is an option for treatment-resistant PTSD. No combination antidepressant regimens are options.
Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents–PTSD section; 2022[16] *Target pediatric population(s): Children and adolescents with PTSD. **Specific target ages for treatments are not provided**.*	
• Medications are only an option (level 3 or level 4) after failure of recommended psychotherapies ○ "There is no empirical evidence to support the use of psychotherapeutic medications in children 6 years or younger" (page 61). This statement is not specific to antidepressants. • Fluoxetine or sertraline are later-line options (level 4) for youth (**no specific age provided)** with PTSD comorbid with a mood disorder; there is little evidence for use of these medications to target core PTSD symptoms in children/adolescents.	• **No information provided about combined antidepressant use in children or adolescents**
Australian Guidelines for the Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder, and Complex PTSD. Chapter 6 Treatment Recommendations; 2021[204] *Target pediatric population(s): Preschool children (birth-5 years), primary school-aged children (6-11 years) and adolescents (12-17 years). "Children and adolescents" = birth to 17 years.[210]*	
• *Insufficient evidence* to form a recommendation about pharmacologic interventions for children and adolescents with PTSD symptoms. Recommended treatments are psychological interventions (eg, trauma-focused CBT). ○ It is suggested to follow depression guidelines if medication is indicated	• **No information provided about combined antidepressant use in children or adolescents**
The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition – Ch. 5 Children and Adolescents; 2021[31] *Target pediatric population(s): Children and adolescents (**specific age range not defined**) with PTSD.*	
• Pharmacotherapy is **not** a recommended treatment for PTSD symptoms in children or adolescents; however, pharmacotherapy may be an option to treat co-occurring conditions. Fluoxetine, paroxetine, and venlafaxine are empirically supported treatment options for adults, but authors point out "None of these agents is currently used to any extent in children and adolescents" (page 568).	• **No information provided about combined antidepressant use in children or adolescents**
International Society for Traumatic Stress Studies (ISTSS); 2019[206] *Target pediatric population(s): Children and adolescents with or at risk (for consideration of preventative treatment) for PTSD. **Specific ages for these pediatric age groups are not provided.***	
• *Insufficient evidence* for treatment of children and adolescents with clinically significant PTSD symptoms with sertraline (no specific age range provided)	• **No information provided about combined antidepressant use in children or adolescents**

[a] *AACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes*

APA: Formal recommendations were based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

ITSS: insufficient evidence indicates the treatment did not separate sufficiently from the comparator by meta-analysis, as evidenced by not meeting the pre-defined clinical significance or overlap of confidence of intervals with the comparator

NICE recommendation strength: Do not Offer: generally, indicates strong recommendation against using the intervention

WFSBP formal recommendations: Strength of recommendation: 1 = strong for; 2 = limited for; 3 = weak for; LOE: A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trial; 4 = no recommendation possible; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias; D = no evidence

Abbreviations: CBT, cognitive behavioral therapy; ISTSS, International Society for Traumatic Stress Studies; LOE, level of evidence; NICE, National Institute for Health and Care Excellence; PTSD, post-traumatic stress disorder; RCT(s), randomized controlled trial(s); SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SSRI(s), selective serotonin reuptake inhibitor(s); WFSBP, World Federation of Societies of Biological Psychiatry

Table 5. Pediatric PTSD Treatment Guideline or Expert Guidance Recommendations: Focus on Indicated Age and Situations for Multiple Antidepressant Therapy

Target Age(s) for Antidepressants and Recommended Antidepressants (recommendation strength/LOE, if provided[a])	Combination Therapy Recommendations (recommendation strength/LOE, if provided[a])
National Institute for Health and Care Excellence (NICE); 2018[205] *Target pediatric population(s): Children and adolescents with or at risk (for consideration of preventative treatment) for PTSD. Strength of recommendations is reflected in the wording of recommendations.*[158]	
• **Medications are not recommended** ("do not offer") for PTSD treatment **in people <18 years old.** • Recommended treatments for children and adolescents 5-17 years old with PTSD include trauma-focused CBT (LOE varies by age and length of time since the causative trauma) • Eye movement desensitization and reprocessing (EMDR) therapy is recommended for ages 7-17 years old, after failure of CBT.	• **No information provided about combined antidepressant use in children or adolescents**

[a] *AACP formal recommendations: strength 2 = there is uncertainty about whether the benefits outweigh the risks; evidence I = most RCT/CCT outcomes used to form the recommendation were considered insufficient, but the certainty of evidence was graded higher (low, moderate, or high) for 2 or more outcomes*

APA: Formal recommendations were based on high-quality SRs and/or meta-analyses. Recommendations are considered strong (recommended) or condition (suggested).

ITSS: insufficient evidence indicates the treatment did not separate sufficiently from the comparator by meta-analysis, as evidenced by not meeting the pre-defined clinical significance or overlap of confidence of intervals with the comparator

NICE recommendation strength: Do not Offer: generally, indicates strong recommendation against using the intervention

WFSBP formal recommendations: Strength of recommendation: 1 = strong for; 2 = limited for; 3 = weak for; LOE: A= strong evidence of benefit, based on ≥2 good-quality RCTs with a placebo control or adequately powered non-inferiority trial and no negative trial; 4 = no recommendation possible; B = limited evidence of benefit, based on 1 placebo-controlled RCT with a moderate risk of bias or 1 RCT without placebo control and no negative studies, or a positive meta-analysis; C = weak evidence of benefit, based on ≥1 non-randomized prospective study of good quality, case-reports with at least 10 patients, or RCT/meta-analytic evidence with a high risk of bias; D = no evidence

Abbreviations: CBT, cognitive behavioral therapy; ISTSS, International Society for Traumatic Stress Studies; LOE, level of evidence; NICE, National Institute for Health and Care Excellence; PTSD, post-traumatic stress disorder; RCT(s), randomized controlled trial(s); SNRI(s), serotonin and norepinephrine reuptake inhibitor(s); SSRI(s), selective serotonin reuptake inhibitor(s); WFSBP, World Federation of Societies of Biological Psychiatry

7.0 SELECT ADDITIONAL SAFETY CONSIDERATIONS

For feasibility, this report does not systematically address safety issues for using antidepressants in youth (please refer to the respective product labeling for drug-specific safety concerns). In addition to some issues addressed in the sections devoted to target mental health conditions (eg, the potential for antidepressant interactions to cause serotonin syndrome), select safety information emerging from the reviewed evidence are:

- Two TCAS are strongly recommended to be avoided (desipramine; high LOE) or used with caution (imipramine; moderate LOE) in children per the "KIDS list" due the risk of sudden cardiac death.[211]
- Refer to Appendix D for contraindications for each antidepressant. Notably, **MAOIs are contraindicated for use with many other antidepressants**, including SSRIs, SNRIs, TCAs, mirtazapine, gepirone, trazodone, nefazodone, and bupropion.[45,46,48,51,53,55-60,63,65,68,78,80,84,88,90,95,97,100,102,106,113,117,119,120]

8.0 SUMMARY

Mental health disorders affect nearly 20% of youth (ie, children and adolescents up to 17 years old) annually in the United States (US).[1] Appropriate treatment of pediatric mental health conditions is important because mental illness is correlated with impaired educational attainment,[6] poorer social relationships,[7] reduced quality of life in adulthood,[7,8] and self-harm.[9-12] In 2021, nearly 20% of surveyed Utah adolescents reported suicidal ideations and 7% had attempted suicide in the past year.[4]

Conditions treatable with antidepressants (eg, depressive disorders, anxiety disorders) are among the most common mental health disorders in youth.[10,12,17,18] Despite the increased prevalence of mental health disorders,[2-4] some evidence suggests many youth do not receive treatment.[3,14] Reasons for possible undertreatment of youth are likely complex, including issues with access to non-pharmacologic psychosocial care (eg, psychotherapy)[15] which is often a first-line treatment for many mental health conditions.[16] Controversies exist with use of antidepressants in youth, such as concerns related to black box warnings for increased suicidality,[21,22] limited evidence leading to off-label use,[21,23] and efficacy or safety concerns.[21,22,24-26] Reports within the past 10 years indicate concerns for both under-[19] and over-utilization[20] of antidepressants in youth.

This report aims to guide appropriate use of antidepressants in Utah Medicaid youth with a focus on the following **3 key objectives:**

1. Identifying on-label (FDA-approved) and compendium-recognized off-label uses of antidepressants in youth and summarizing recent guideline/guidance statements on the place-in-therapy of antidepressants for target conditions.
2. Summarizing indicated ages for use of antidepressants per compendia and recent guidelines/guidance statements.
3. Describing expert opinion or evidence regarding concurrent use of antidepressants (multiple antidepressant therapy [MAT]) for target conditions in youth.

Recent (2018-2013) clinical practice guideline or guidance statements included for the key objectives are those addressing antidepressant treatment for depressive disorders, anxiety disorders, obsessive-

compulsive disorder (OCD), or post-traumatic stress disorder (PTSD), which we refer to collectively as the target conditions.

Thirty-six unique active ingredients classified as an antidepressant by the compendia Lexicomp (see **Appendix A Table A1**) are addressed by this report. Antidepressants are heterogeneous, with unique pharmacology even among those within the same drug class. Notably, most classes of antidepressants boost serotonergic neurotransmission, including the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs),[38] and monoamine oxidase inhibitors (MAOIs),[212] among others. Newer antidepressant classes (ie, N-methyl-D-aspartate [NDMA] receptor antagonists and gamma-aminobutyric acid [GABA] modulators)[39-42] and the dopamine and norepinephrine reuptake inhibitor (DNRI), bupropion,[43] primarily produce non-serotonergic effects. Although many antidepressants are available in multiple formulations, for simplicity, throughout this report, we primarily address antidepressants by active ingredient.

Key Question 1: FDA-Approved or Compendia-Recognized Antidepressant Uses in Pediatrics, and Guideline Place-in-Therapy for Target Conditions

Antidepressants as a class may be used to treat many pediatric mental health or other conditions according to the drug compendia, Lexicomp and Micromedex. There are fewer FDA-approved pediatric indications for antidepressants than potential off-label uses[***]. Potential uses vary by antidepressant, sometimes according to the unique formulations for the same active ingredient[†††], and by age.

Regarding FDA-approved uses,

- At least 1 antidepressant is FDA approved to treat the following mental health conditions in youth:
  - depressive disorders including major depressive disorder (SSRIs, fluoxetine and escitalopram)[51,55]; depression with or without other comorbidities (several TCAs and the MAOI, isocarboxazid)[56-59,61]; bipolar depression (fluoxetine with olanzapine)[51]; and postpartum depression (GABA modulator, brexanolone)[62];
  - anxiety disorders including generalized anxiety disorder (SSRI, escitalopram; SNRI, duloxetine)[55,63]; anxiety or anxiety associated with alcoholism (doxepin)[57]; and
  - OCD (SSRIs, fluoxetine, fluvoxamine, and sertraline; and TCA, clomipramine).[51,53,64,65]
- Non-mental health conditions with FDA-approval for treatment with at least 1 antidepressant in pediatrics include fibromyalgia (duloxetine),[63] nocturnal enuresis (imipramine),[48] and general anesthesia or procedural sedation (ketamine).[54]

Most off-label uses (per Micromedex) are supported by level B evidence (eg, non-randomized studies or low-quality randomized controlled trials [RCTs]), and some off-label uses are based on expert opinion only. Only 3 off-label uses received level A ratings (good quality RCTs), with evidence favoring efficacy per Micromedex: sertraline for generalized anxiety disorder (GAD), bupropion for attention-deficit/hyperactivity disorder (ADHD), and ketamine for moderate to severe acute pain.[45,53,54]

[***] Summarized compendia-recognized off-label uses include those rated as "recommended" by Micromedex, which sometimes includes indications with inconclusive efficacy, and any use by Lexicomp. See **Appendix E** for details about evidence ratings for off-label uses by Micromedex.

[†††] Recognized uses are summarized by antidepressant active ingredient, not specific formulation. Refer to **Appendix D** and **Appendix E** for details about uses by unique antidepressant formulation.

Nonetheless, experts recognize the necessity of using antidepressants off-label for many mental health conditions in children or adolescents due to the paucity of registered trials needed for FDA approval.[35]

- Potential off-label mental health indications[‡‡‡] for pediatrics per compendia (Micromedex and/or Lexicomp) for 1 or more antidepressants include (see Table 1 and section 4 for details):
  - treatment-refractory depression, or atypical or non-endogenous depression
  - anxiety disorders including panic disorder, social anxiety disorder, separation anxiety disorder, and selective mutism
  - eating disorders including bulimia nervosa or anorexia nervosa
  - insomnia/sleep disturbances
- Additional potential off-label, non-mental health indications for at least 1 antidepressant in youth (see Table 1) per pharmacy compendia include: migraines or headache prophylaxis treatment; cyclic vomiting syndrome; irritable bowel syndrome; urinary incontinence; neuropathic or acute pain; and smoking cessation.

Generally, first-line treatment for pediatric depressive disorders, anxiety disorders, and OCD depends on disease severity and age. Non-pharmacologic therapies (eg, psychoeducation or psychotherapy) are often recommended first-line for mild to moderate severity and in younger children,[16,44,86,127-129,163] while medication with or without psychotherapy is recommended for moderate to severe cases.[16,44,127-129,163,177] SSRIs are recommended as first line pharmacotherapy for depressive disorders and OCD.[16,18,86,131,178] For most anxiety disorders, SSRIs or SNRIs (duloxetine or venlafaxine) are options,[17,163,164] with higher levels of evidence available to support SSRI therapy than SNRIs.[17,164] Antidepressants are not recommended for treating pediatric PTSD core symptoms (eg, intrusive memories, avoidance, and/or hypervigilance[207]) due to insufficient evidence.[16,31,204-206] Recommendations and/or level of evidence supporting a particular SSRI or SNRI varies by condition. Refer to sections 6.2 to 6.5 for details on treatment of target pediatric mental health conditions.

Pediatric guideline recommendations favoring SSRIs and sometimes SNRIs as first line pharmacotherapy are generally in agreement with compendia-recognized uses suggesting that SSRIs may be used for more mental health indications than other drug classes. All SSRIs except vilazodone and vortioxetine have at least 1 compendia-recognized pediatric indication,[51,53,55,64,66,67,71,78-82,87-90] whereas, among SNRIs, only duloxetine and vortioxetine have potential pediatric uses.[63,68,69,96-102] Fluoxetine is an option for more pediatric mental health disorders than other SSRIs, having guideline- and compendia-recognized uses for depressive disorders, anxiety disorders, and OCD, as well as being the only compendia-recognized antidepressant option for pediatric selective mutism and eating disorders.[18,51,79,86]

Many antidepressants lack evidence for use in children or adolescents per major compendia (see Table 1). The following antidepressants or antidepressant classes are <u>suggested to be avoided</u> in pediatric patients by 1 or more guidelines or expert guidance statements:

- Compared to SSRIs and SNRIs, older antidepressants, including TCAs and MAOIs have a less favorable safety profile.[35,44]

[‡‡‡] Terminology for off-label uses is per compendia (Lexicomp and/or Micromedex), which may not align with current expert opinion or guideline definitions. For example, it is unclear if "treatment-refractory" per compendia aligns with expert opinion on the definition of treatment-refractory versus treatment-resistant depression.

- TCAs (except clomipramine) and MAOIs (except transdermal selegiline) are not recommended for youth by the Texas guidance.[35]
- There is insufficient evidence to use TCAs or MAOIs (or SNRIs) for pediatric major depressive disorder (MDD)[18] or to use TCAs for anxiety disorders, per the American Academy of Child and Adolescent Psychiatry (AACAP).[17] Other depression guidelines recommend against TCAs for all youth,[127] or for pre-school age children specifically.[16]
- Imipramine and clomipramine are recommended against use for pediatric depression by the American Psychological Association (APA).
- TCAs, imipramine and desipramine, are on the KIDs list of drugs to avoid in children due to an increased risk for sudden cardiac death.[211] [131]

- Venlafaxine may increase the risk for harm,[35] including having a possibly higher risk of suicide than other SNRIs.[17] The APA and National Institute for Health and Care Excellence (NICE) recommend against using it for pediatric MDD.[18,131] Nonetheless, other guideline(s) recognize venlafaxine as an option (later-line) for depression[16] and an option for some anxiety disorders.[16,17,31,163,164]
- Paroxetine may carry a higher risk of suicidality than other SSRIs[17] and users may suffer significant discontinuation withdrawal symptoms.[18] Some guidelines recommend against or do not include paroxetine among suggested SSRIs for pediatric depressive disorders,[18,127,131] anxiety disorders,[163] OCD,[31] or in general.[35] Florida guidance took the approach of recommending paroxetine as a later-line option for depression or anxiety due to its safety profile and recommending against its use in preschool-aged children.[16]
- Other antidepressants not recommended include mirtazapine for depressive disorders in youth,[131] bupropion in preschool aged children,[27] and vortioxetine and levomilnacipran due to insufficient evidence.[35]

Key Question 2: Compendia- and Guideline-suggested Minimum Ages to Receive an Antidepressant

Compendia and reviewed guideline/expert guidance statements show there is little robust evidence to support use of antidepressants in children younger than about 6 to 7 years old.[16,164,178,213] Six years old is the youngest FDA-approved age for any antidepressant, including for sertraline (SSRI) for the treatment of OCD[53,67] and imipramine (TCA) for the treatment of nocturnal enuresis.[48,73] The youngest age of compendia-recognized off-label uses varies by indication and antidepressant; generally, the youngest ages are 5 to 6 years old. Among SSRIs, fluoxetine is the agent with youngest suggested off-label age of 5 years old for a selective mutism.[79] Other antidepressants with possible off-label uses for those under 5 years old are ketamine for anesthesia/rapid intubation (age ≥ 0)[54] and trazodone for sleep disturbances (age ≥ 18 months).[83]

Only a few reviewed recent (2018-2023) guidelines/guidance statements provide specific ages for formal antidepressant recommendations. The AACAP guideline for the treatment of MDD states that most RCT evidence involves adolescents, and that studies among children primarily included youth 7 to 11 years old.[18] The youngest suggested age is 4 years old (per Florida guidance),[16] and 5 years old is the minimum suggested age by 2 international guidelines (NICE and a Korean guidance).[127,132] Evidence for using SSRIs or SNRIs for anxiety disorders is most applicable to ages ≥ 8 years old, but the AACAP recommends either option for children as young as 6 years old.[17] Less age-specific guidance is provided regarding the

treatment of OCD with antidepressants. Most RCT evidence (primarily for SSRIs) is for children 7-8 years old with OCD,[178] and guidance from Florida considers select SSRIs and clomipramine options for children ages 6 or older.[16]

Guidelines specifically addressing use of antidepressants for preschool-aged children (eg, less than 6 years old), including an older prescribing algorithm by Gleason et al (2007),[27] tend to suggest using psychosocial treatment concurrently with medication when it is decided that an antidepressant is necessary.[16,27] Gleason et al suggested considering antidepressants for preschool-aged children only if they have continued functional impairment after treatment with evidence-based psychosocial therapy.[27] Fluoxetine is the first-line antidepressant suggested for very young children with MDD or an anxiety disorder,[16,27] and is also among first-line options for OCD (fluvoxamine or sertraline are also options).[27] Florida guidance suggests not using psychotherapeutic medications for almost all children under 24 months old, with rare exceptions.[16] Use of an antidepressant among youth under 4 years of age is a suggested criterion for additional review of the child's clinical status by Texas expert guidance.[35]

Key Question 3: Multiple Antidepressant Therapy (MAT) in Pediatrics

No systematic review focused on MAT in youth was found. One non-systematic review from 2014 addressed antidepressant polypharmacy (ie, antidepressant use with any other psychotropic agent) specifically.[34] All other evidence was incidentally discovered from expert opinion reviews, many of which were published in 2015 or earlier. While we cannot be sure that we captured all pediatric MAT evidence (eg, individual observational studies), the minimal evidence found by our literature review is congruent with the deficit of MAT evidence cited by recent guidelines for the treatment of pediatric depression, anxiety, OCD and PTSD.

Based on recent (2018-2023) US or international guidelines, as well as expert treatment guidance statements, MAT with select combinations *may* have a place in therapy for treatment-resistant MDD[16,130,132] or OCD,[16,86,138,177] and possibly, anxiety disorders,[16] in select youth.[16] MAT is not listed as an option for pediatric PTSD.[16,31,178,204-206]

Often, guidelines or guidance statements suggested MAT as an option in the setting of *augmentation* therapy (ie, adding a second antidepressant when there is an insufficient response to the first),[16,130,134,179] not *combination* therapy (ie, starting 2 antidepressants concurrently prior to monotherapy failure). Older expert opinion reviews also recognize the option to add another antidepressant to temporarily address insomnia, or to help manage side effects of an efficacious antidepressant.[24,142]

Regardless, antidepressant combinations should be selected carefully, with consideration to each agent's pharmacology and potential for drug-drug interactions. Combining antidepressants with strong serotonergic activity (eg, SSRI+MAOI) is not advised due to the risk of serotonin syndrome.[18,129,140] The following bullets summarize antidepressant combination options based on expert opinion, or those with limited empirical support:

- For **pediatric MDD**, 3 of 11 guidelines/expert guidance statements mention the option for MAT,[16,130,132] but the AACAP (2023) believes there is insufficient evidence to guide MAT.[18]
    - When particular combinations are specified, the options listed are to combine an **SSRI with bupropion** or **mirtazapine**, based on extrapolating non-controlled clinical trial or RCT evidence

from adults.[134,143] However, an expert recently questioned mirtazapine *augmentation* (for adults) due to conflicting and limited evidence of benefits.[143]

- In 1 RCT each, primarily among adolescents with MDD, oral antidepressants have been used concurrently with **trazodone** (for sleep issues) and **esketamine** (for additive antidepressant effect; in process study)**.**[141,150] Based on a *post-hoc* observational analysis of an RCT, the combination of trazodone with an SSRI (fluoxetine or paroxetine) was associated with reduced antidepressant efficacy among the 33 adolescents who received that combination versus other participants who received another agent for insomnia (eg, antihistamine or non-benzodiazepine GABA modulator).[141] Results are not yet available for the esketamine RCT, which included youth 9-17 years old with MDD at high risk for suicide.[150]
- Intravenous **ketamine** has been given to adolescents (13 to 18 years) receiving stable oral antidepressants, including an SNRI, bupropion, or SSRI, in case reports, in a single arm trial (about 11 youth total), and in 1 cross-over RCT.[149,153,155,156] In general, the clinical trials and case reports suggest ketamine (± oral antidepressant) may be effective and is tolerated by most patients. However, no trial compared the results of ketamine monotherapy to ketamine + antidepressant therapy, limiting interpretations about the combination.

- For **pediatric patients (6-17 years old) with an anxiety disorder** and partial response to SSRI or SNRI monotherapy, one guideline (of 7 total reviewed) mentioned the option to augment with the TCA, clomipramine.[16] However, no empirical evidence in pediatrics or adults with an anxiety disorder was cited to support this combination (SSRI or SNRI + clomipramine).
  - Another anxiety guideline advised avoiding combination pharmacotherapy in general (no specific age or drug combinations mentioned), even for treatment-resistant cases, due to a lack of evidence for benefit.[165]
- Most reviewed guidelines (4 of 6) recognize the option to augment SSRI therapy with the non-selective serotonin-reuptake inhibitor, **clomipramine**, to boost serotonergic neurotransmission in the setting of **resistant or difficult-to-treat OCD**.[16,86,138,177] This option is suggested based on expert opinion[86] and 2 small case series (n=9 total) of pediatric patients (ages 9-17) that received sertraline (50-200 mg daily) or fluoxetine (20 to 60 mg daily) with clomipramine (about 25 to 75 mg daily). Results suggested increased efficacy with combination therapy in most cases.[183,184] However, tolerability of clomipramine + SSRI was variable: 2 cases experienced cardiotoxicity (QT prolongation ± tachycardia), leading to discontinuation for 1 patient.[184] While the limited pediatric evidence is for sertraline or fluoxetine,[183,184] some guidelines suggest combining clomipramine with fluvoxamine[44,177] due to a more favorable pharmacokinetic interaction that may boost clomipramine exposure levels and reduce levels of the more toxic clomipramine metabolite.[179]
  - An older (2005) expert opinion review also suggested the option to combine SSRIs or an SSRI+SNRI for treatment-resistant pediatric OCD, but no empiric evidence was cited to support this option.[180]

Few guidelines or guidance statements provide details about when and how to initiate MAT, likely due to the paucity of high-quality evidence to guide treatment of resistant cases in general[134] and the lack of evidence for MAT specifically. Several guidelines or experts advise only considering combined psychotropic therapy after confirming the accuracy of the diagnosis for the patient's condition/symptom, in addition to compliance with and appropriate intensity of prior therapies (psychotherapy and drug).[16,130,134,177] MAT is usually only one of multiple combination therapy options

suggested for difficult-to-treat depression or OCD; other options are second-generation antipsychotics for OCD or MDD, along with lithium, thyroxine and others for MDD.[16,31,86,130,134,138] Prescribing ≥2 antidepressants concurrently is not automatically inappropriate but should prompt a careful review of the patient's clinical status, according to the Texas guidance.[35] General good practices are to start one medication at time,[35] document the rationale and planned duration for the combination therapy trial, and to select a combination supported by clinical rationale or scientific literature.[33] Safety and efficacy of MAT should be monitored closely. When using clomipramine with an SSRI, monitoring for cardiotoxicity and serotonin syndrome is required.[44,179]

In conclusion, antidepressants are options for treating many pediatric mental and non-mental health conditions. There are more compendia-recognized off-label uses for antidepressants than FDA-approved uses, with most of the off-label uses supported by lower-quality studies or expert opinion. SSRIs have the most FDA-approved and compendia- or guideline-recognized uses and are among first line treatment options for pediatric MDD, anxiety disorders, and OCD in children aged approximately 6 years or older. Evidence is insufficient to support using antidepressants for core PTSD symptoms in pediatrics. MAT with select combinations may be a treatment option for youth with treatment-resistant or difficult-to-treat MDD or OCD. Given the limited evidence and potential for harm, antidepressant combinations should be selected carefully based on scientific evidence or clinical rationale and monitored closely for efficacy and safety.

REFERENCES

1. National Alliance on Mental Illness. Mental Health by the Numbers. 2023. Last Updated April 2023. Accessed October 18, 2023. Available at https://www.nami.org/mhstats

2. Bitsko RH, Claussen AH, Lichstein J, et al. Mental Health Surveillance Among Children - United States, 2013-2019. *MMWR*. 2022;71(Suppl-2):1-42. doi:http://dx.doi.org/10.15585/mmwr.su7102a1

3. Agency for Healthcare Research and Quality. Child and Adolescent Mental Health. *2022 National Healthcare Quality and Disparities Report*. 2022. Accessed October 18, 2023. Available at https://www.ncbi.nlm.nih.gov/books/NBK587174/

4. Utah Department of Health Bureau of Health Promotion. *2021 Utah Adolescent Health Report*. Health UDo; 2022: 92 pages. Accessed October 18, 2023. Available at https://health.utah.gov/wp-content/uploads/2021-Utah-Adolescent-Health-Report.pdf

5. Lebrun-Harris LA, Ghandour RM, Kogan MD, Warren MD. Five-Year Trends in US Children's Health and Well-being, 2016-2020. *JAMA Pediatr*. 2022;176(7):e220056. doi:10.1001/jamapediatrics.2022.0056

6. Youth.Gov. How Mental Health Disorders Affect Youth. Accessed October 18, 2023. Available at https://youth.gov/youth-topics/youth-mental-health/how-mental-health-disorders-affect-youth

7. Chen H, Cohen P, Kasen S, Johnson JG, Berenson K, Gordon K. Impact of Adolescent Mental Disorders and Physical Illnesses on Quality of Life 17 Years Later. *Archives of Pediatrics & Adolescent Medicine*. 2006;160(1):93-99. doi:10.1001/archpedi.160.1.93

8. Schlack R, Peerenboom N, Neuperdt L, Junker S, Beyer AK. The effects of mental health problems in childhood and adolescence in young adults: Results of the KiGGS cohort. *J Health Monit*. 2021;6(4):3-19. doi:10.25646/8863

9. American Psychiatric Association. What is Obsessive-Compulsive Disorder? . Psychiatry.org. 2022. Last Updated October 2022. Accessed October 16, 2023. Available at https://www.psychiatry.org/patients-families/obsessive-compulsive-disorder/what-is-obsessive-compulsive-disorder

10. American Psychiatric Association. Depressive Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition, Text Revision ed. American Psychiatric Association 2022. Accessed October 23, 2023

11. American Psychiatric Association. Trauma- and Stressor-Related Disorders. *Diagnostic and Statistical Menutal of Mental Disorders*. Fifth Edition, Text Revision ed. American Psychiatric Association 2022. Accessed October 26, 2023

12. American Psychiatric Association. Anxiety Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition, Text Revision ed. American Psychaitric Association 2022. Accessed November 3, 2023

13. America's Health Rankings. Teen Suicide in Utah. 2021. Accessed November 21, 2023. Available at https://www.americashealthrankings.org/explore/measures/teen_suicide/UT

14. Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part I. Practice Preparation, Identification, Assessment, and Initial Management. *Pediatrics*. 2018;141(3):e20174081. doi:10.1542/peds.2017-4081

15. Summers L, Meppen D, Ball S. *Utah's Mental Health System. A collaborative endeavor of the Kem C. Gardner Policy Institute and the Utah Hospital Association.* . Institute KCGP; 2019: 40 pages. Last Updated August 2019. Accessed November 7, 2023. Available at https://gardner.utah.edu/wp-content/uploads/MentalHealthReportAug2019.pdf

16. Florida Center for Behavioral Health Improvements and Solutions. *2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolesents*. 2022: 72 pages. Last Updated June 2022. Accessed September 26, 2023. Available at https://floridabhcenter.org/wp-content/uploads/2022/06/Full-Set_2022-06-FL-Best-Practice-Medication-Child-Adolescent-FINAL_06-14-22-1.pdf

17. Walter HJ, Bukstein OG, Abright AR, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2020;59(10):1107-1124. doi:https://dx.doi.org/10.1016/j.jaac.2020.05.005

18. Walter HJ, Abright AR, Bukstein OG, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Major and Persistent Depressive Disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2023;62(5):479-502. doi:https://dx.doi.org/10.1016/j.jaac.2022.10.001

19. Merikangas KR, He JP, Rapoport J, Vitiello B, Olfson M. Medication use in US youth with mental disorders. *JAMA Pediatr*. 2013;167(2):141-148. doi:10.1001/jamapediatrics.2013.431

20. Cosgrove L, Morrill Z, Yusif M, et al. Drivers of and Solutions for the Overuse of Antidepressant Medication in Pediatric Populations. *Front Psychiatry*. 2020;11:17. doi:10.3389/fpsyt.2020.00017

21. Dwyer JB, Bloch MH. Antidepressants for Pediatric Patients. *Curr Psychiatr*. 2019;18(9):26-42f.

22. Masi G. Controversies in the Pharmacotherapy of Adolescent Depression. *Current pharmaceutical design*. 2022;28(24):1975-1984. doi:https://dx.doi.org/10.2174/1381612828666220526150153

23. Lam MK, Lam LT, Butler-Henderson K, et al. Prescribing behavior of antidepressants for depressive disorders: A systematic review. *Frontiers in psychiatry*. 2022;13:918040. doi:https://dx.doi.org/10.3389/fpsyt.2022.918040

24. Choe CJ, Emslie GJ, Mayes TL. Depression. *Child and adolescent psychiatric clinics of North America*. 2012;21(4):807-829. doi:https://dx.doi.org/10.1016/j.chc.2012.07.002

25. Strawn JR, Mills JA, Poweleit EA, Ramsey LB, Croarkin PE. Adverse Effects of Antidepressant Medications and their Management in Children and Adolescents. *Pharmacotherapy*. 2023;43(7):675-690. doi:10.1002/phar.2767

26. Stutzman DL. Long-term use of antidepressants, mood stabilizers, and antipsychotics in pediatric patients with a focus on appropriate deprescribing. *Ment Health Clin*. 2021;11(6):320-333. doi:10.9740/mhc.2021.11.320

27. Gleason MM, Egger HL, Emslie GJ, et al. Psychopharmacological treatment for very young children: contexts and guidelines. *J Am Acad Child Adolesc Psychiatry*. 2007;46(12):1532-1572. doi:10.1097/chi.0b013e3181570d9e

28. Whalen DJ, Sylvester CM, Luby JL. Depression and Anxiety in Preschoolers: A Review of the Past 7 Years. *Child Adolesc Psychiatr Clin N Am*. 2017;26(3):503-522. doi:10.1016/j.chc.2017.02.006

29. Kafali N, Progovac A, Hou SS, Cook BL. Long-Run Trends in Antidepressant Use Among Youths After the FDA Black Box Warning. *Psychiatr Serv*. 2018;69(4):389-395. doi:10.1176/appi.ps.201700089

30. Zito JM, Pennap D, Safer DJ. Antidepressant Use in Medicaid-Insured Youth: Trends, Covariates, and Future Research Needs. *Frontiers in Psychiatry*. 2020;11doi:10.3389/fpsyt.2020.00113 https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00113

31. Taylor DM, Barnes TRE, Young AH. Ch. 5 Children and adolescents. *The Maudsley Prescribing Guidelines in Psychiatry* 14th ed. John Wiley & Sons, Inc. ; 2021.

32. Soria Saucedo R, Liu X, Hincapie-Castillo JM, Zambrano D, Bussing R, Winterstein AG. Prevalence, Time Trends, and Utilization Patterns of Psychotropic Polypharmacy Among Pediatric Medicaid Beneficiaries, 1999-2010. *Psychiatr Serv*. 2018;69(8):919-926. doi:10.1176/appi.ps.201700260

33. Jureidini J, Tonkin A, Jureidini E. Combination pharmacotherapy for psychiatric disorders in children and adolescents: prevalence, efficacy, risks and research needs. *Paediatr Drugs*. 2013;15(5):377-391. doi:10.1007/s40272-013-0032-6

34. Diaz-Caneja CM, Espliego A, Parellada M, Arango C, Moreno C. Polypharmacy with antidepressants in children and adolescents. *The international journal of neuropsychopharmacology*. 2014;17(7):1063-1082. doi:https://dx.doi.org/10.1017/S1461145712001265

35. The Parameters Workgroup of the Psychiatric Executive Formulary Committee. *Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health (6th Version)*. Texas Health and Human Services; 2019: 65 pages. Last Updated June 2019. Accessed September 21, 2023. Available at https://www.hhs.texas.gov/sites/default/files/documents/doing-business-with-hhs/provider-portal/facilities-regulation/psychiatric/psychotropic-medication-utilization-parameters.pdf

36. Canada's Drug and Health Technology Agency (CADTH). Guidelines – Broad – MEDLINE, Embase, PsycInfo. CADTH Search Filters Database; 2021. Last Updated December 9, 2021. Accessed September 12, 2023. Available at https://searchfilters.cadth.ca/link/26

37. McMaster University Health Information Research Unit. Sarch Filters for Medline in Ovid Syntax and the Pubmed Translation. 2022. Accessed November 7, 2022. Available at https://hiruweb.mcmaster.ca/hkr/hedges/medline/

38. Moraczewski J, Awosika AO, Aedma KK. *Tricyclic Antidepressants*. StatPearls Publishing; 2023. Accessed November 9, 2023. Available at https://www.ncbi.nlm.nih.gov/books/NBK557791/

39. Par pharmaceutical. Ketamine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 20, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

40. Janssen Pharmaceuticals Inc. Esketamine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 31, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

41. Sage Therapeutics Inc. Brexanolone. Lexi-Drugs. Lexicomp.com; 2023. Last Updated September 13, 2023. Accessed October 6, 2023. Available at http://online.lexi.com

42. Biogen Inc. Zuranolone. Lexi-Drugs. Lexicomp.com; 2023. Last Updated August 7, 2023. Accessed October 6, 2023. Available at http://online.lexi.com

43. GlaxoSmithKline. Bupropion. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

44. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(1):98-113. doi:10.1016/j.jaac.2011.09.019

45. GlaxoSmithKline. Bupropion HCl. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

46. Bausch Health US LLS. Bupropion hydrobromide. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

47. Mallinckrodt Inc. Imipramine Pamoate. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

48. Mallinckrodt Inc. Imipramine hydrocholoride. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

49. Mylan Pharmaceuticals Inc. Perphenazine/Amitriptyline. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated October 19, 2023. Accessed October 30, 2023. Available at https://www.micromedexsolutions.com

50. Mylan Pharmaceuticals Inc. Chlordiazepoxide/Amitriptyline. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated October 19, 2023. Accessed October 30, 2023. Available at https://www.micromedexsolutions.com

51. Lilly USA LLC. Fluoxetine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

52. Axsome Therapeutics Inc. Dextromethorphan-bupropion. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

53. Pfizer Inc. Sertraline. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

54. Par pharmaceutical. Ketamine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed October 6, 2023. Available at https://www.micromedexsolutions.com

55. Abbvie Inc. Escitalopram. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

56. Sandoz. Amitriptyline. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

57. Samaxon Pharmaceuticals. Doxepin. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

58. Mallinckrodt Inc. Nortriptyline. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

59. Duramed Pharmaceuticals Inc. Protriptyline. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

60. Teva Pharmaceuticals. Trimipramine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

61. Validus Pharmaceuticals LLS. Isocarboxazid. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

62. Sage Therapeutics Inc. Brexanolone. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated March 29, 2023. Accessed October 6, 2023. Available at https://www.micromedexsolutions.com

63. Eli Lilly and Company. Duloxetine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

64. Pharma ULC. Fluvoxamine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed Ocrober 6, 2023. Available at https://www.micromedexsolutions.com

65. Mallinckrodt Inc. Clomipramine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

66. Pharma ULC. Fluvoxamine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 26, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

67. Pfizer Inc. Sertraline. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 30, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

68. Wyeth Pharmaceuticals LLC. Venlafaxine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

69. Wyeth Pharmaceuticals LLC. Venlafaxine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

70. Concordia Pharmaceuticals Inc. Tranylcypromine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated October 4, 2023. Accessed October 6, 2023. Available at https://www.micromedexsolutions.com

71. Allergan USA Inc. Citalopram. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

72. Sanofi-Aventis U.S. LLC. Desipramine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

73. Mallinckrodt Inc. Imipramine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

74. Samaxon Pharmaceuticals. Doxepin. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

75. Mallinckrodt Inc. Nortriptyline. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

76. Bausch Health US LLC. Selegiline. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

77. Parke-Davis. Phenelzine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

78. Allergan USA Inc. Citalopram. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

79. Lilly USA LLC. Fluoxetine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

80. Apotex Corp. Paroxetine HCl. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

81. Abbvie Inc. Escitalopram. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

82. Apotex Corp. Paroxetine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

83. Fera Pharamceuticals. Trazodone. Lexi-Drugs. Lexicomp. com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

84. Sanofi-Aventis U.S. LLC. Desipramine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

85. Sandoz. Amitriptyline. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

86. Weidle B, Ivarsson T, Asbahr FR, et al. Specialty knowledge and competency standards for pharmacotherapy for pediatric obsessive-compulsive disorder. *Psychiatry research*. 2021;299:113858. doi:https://dx.doi.org/10.1016/j.psychres.2021.113858

87. Allergan USA Inc. Vilazodone. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 20, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

88. Allergan USA Inc. Vilazodone. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

89. Takeda Pharmaceuticals America Inc. Vortioxetine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 25, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

90. Takeda Pharmaceuticals America Inc. Vortioxetine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

91. Mallinckrodt Inc. Clomipramine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

92. Duramed Pharmaceuticals Inc. Protriptyline. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

93. Teva Select Brands. Trimipramine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

94. Mylan Specialty LP. Selegiline Transdermal. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

95. Noven Therapeutics LLC. Paroxetine Mesylate. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

96. Pernix Therapeutics LLC. Desvenlafaxine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

97. Pernix Therapeutics LLC. Desvenlafaxine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 20, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

98. Eli Lilly and Company. Duloxetine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 2, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

99. Abbvie Inc. Levomilnacipran. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

100. Abbvie Inc. Levomilnacipran. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 19, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

101. Allergan USA Inc. Milnacipran. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

102. Allergan USA Inc. Milnacipran. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

103. Myan Pharmaceuticals Inc. Amitriptyline-Chlordiazepoxide. Lexi-Drugs. Lexicomp.com; 2023. Last Updated Octover 17, 2023. Accessed October 31, 2023. Available at http://online.lexi.com

104. Mylan Pharmaceuticals Inc. Amitriptyline-Perphenazine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed October 31, 2023. Available at http://online.lexi.com

105. Actavis Pharma Inc. Amoxapine. Lexi-Drugs. Lexicomp. Waltham, MA: UpToDate, Inc.; 2023. Last Updated October 27, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

106. Actavis Pharma Inc. Amoxapine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

107. Validus Pharmaceuticals LLS. Isocarboxazid. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

108. Parke-Davis. Phenelzine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

109. Bausch Health US LLS. Selegiline Oral. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

110. Concordia Pharmaceuticals Inc. Tranylcypromine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 17, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

111. Axsome Therapeutics Inc. Dextromethorphan-bupropion. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed October 6, 2023. Available at https://www.micromedexsolutions.com

112. Janssen Pharmaceuticals Inc. Esketamine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated August 28, 2023. Accessed October 6, 2023. Available at https://www.micromedexsolutions.com

113. Company MP. Gepirone. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated October 28,2023. Accessed October 30, 2023. Available at https://www.micromedexsolutions.com

114. Mission Pharmacal Company. Gepirone. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 27,2023. Accessed October 31, 2023. Available at http://online.lexi.com

115. EXXUA (gepirone) extended-release tablets, for oral use. Package insert. Mission Pharmacal Company; 2023. Accessed October 6, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2f2db2f5-49d3-4d47-a08a-628df49d2120

116. Merck & Co Inc. Mirtazapine. Lexi-Drugs. Lexicomp.com; 2023. Last Updated October 18,2023. Accessed November 2, 2023. Available at http://online.lexi.com

117. Merck & Co Inc. Mirtazapine. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

118. Teva Pharmaceuticals. Nefazodone. Lexi-Drugs. Lexicomp.com; 2023. Last Updated November 1, 2023. Accessed November 2, 2023. Available at http://online.lexi.com

119. Teva Pharmaceuticals. Nefazodone. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

120. Fera Pharamceuticals. Trazodone. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 25, 2023. Accessed September 27, 2023. Available at https://www.micromedexsolutions.com

121. Biogen Inc. Zuranolone. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated August 28, 2023. Accessed October 6, 2023. Available at https://www.micromedexsolutions.com

122. Weihs KL, Murphy W, Abbas R, et al. Desvenlafaxine Versus Placebo in a Fluoxetine-Referenced Study of Children and Adolescents with Major Depressive Disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):36-46. doi:10.1089/cap.2017.0100

123. Atkinson S, Lubaczewski S, Ramaker S, et al. Desvenlafaxine Versus Placebo in the Treatment of Children and Adolescents with Major Depressive Disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):55-65. doi:10.1089/cap.2017.0099

124. Durgam S, Chen C, Migliore R, Prakash C, Edwards J, Findling RL. A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Vilazodone in Adolescents with Major Depressive Disorder. *Paediatr Drugs*. 2018;20(4):353-363. doi:10.1007/s40272-018-0290-4

125. Kratochvil CJ, Newcorn JH, Arnold LE, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. *J Am Acad Child Adolesc Psychiatry*. 2005;44(9):915-924. doi:10.1097/01.chi.0000169012.81536.38

126. Ghandour RM, Sherman LJ, Vladutiu CJ, et al. Prevalence and Treatment of Depression, Anxiety, and Conduct Problems in US Children. *J Pediatr*. 2019;206:256-267.e253. doi:10.1016/j.jpeds.2018.09.021

127. National Institute for Health and Care Excellence (NICE). *Depression in children and young people: identification and management*. 2019: 49 pages. Last Updated June 25, 2019. Available at https://www.nice.org.uk/guidance/ng134/resources/depression-in-children-and-young-people-identification-and-management-pdf-66141719350981

128. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *The Australian and New Zealand journal of psychiatry*. 2021;55(1):7-117. doi:https://dx.doi.org/10.1177/0004867420979353

129. Cheung AH, Zuckerbrot RA, Jensen PS, Laraque D, Stein REK. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part II. Treatment and Ongoing Management. *Pediatrics*. 2018;141(3)doi:https://dx.doi.org/10.1542/peds.2017-4082

130. Grover S, Avasthi A. Clinical Practice Guidelines for the management of depression in children and adolescents. *Indian journal of psychiatry*. 2019;61(Suppl 2):226-240. doi:https://dx.doi.org/10.4103/psychiatry.IndianJPsychiatry_563_18

131. Guideline Development Panel for the Treatment of Depressive Disorders. *APA Clinical Practice Gudieline for the Treatment of Depression Across Three Age Cohorts*. American Psychological Association; 2019: 86 pages. Accessed September 25, 2023. Available at https://www.apa.org/depression-guideline/guideline.pdf

132. Seo JS, Bahk W-M, Woo YS, et al. Korean Medication Algorithm for Depressive Disorder 2021, Fourth Revision: An Executive Summary. *Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology*. 2021;19(4):751-772. doi:https://dx.doi.org/10.9758/cpn.2021.19.4.751

133. Strawn JR, Aaronson ST, Elmaadawi AZ, et al. Treatment-Resistant Depression in Adolescents: Clinical Features and Measurement of Treatment Resistance. *J Child Adolesc Psychopharmacol*. 2020;30(4):261-266. doi:10.1089/cap.2020.0008

134. Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual Research Review: Defining and treating pediatric treatment-resistant depression. *Journal of child psychology and psychiatry, and allied disciplines*. 2020;61(3):312-332. doi:https://dx.doi.org/10.1111/jcpp.13202

135. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *Jama*. 2008;299(8):901-913. doi:10.1001/jama.299.8.901

136. Royal College of Psychiatrists. *Position statement on antidepressants and depression*. PS04/19. 2019: 29 pages. Accessed September 25, 2023. Available at https://www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/position-statements/ps04_19---antidepressants-and-depression.pdf?sfvrsn=ddea9473_5

137. Viswanathan M, Kennedy SM, McKeeman J, et al. *Treatment of Depression in Children and Adolescents: A Systematic Review. Comparative Effectiveness Review No. 224. (Prepared by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-2015-00011-I*. AHRQ Publication No. 20-EHC005-EF. Agency for Healthcare Research and Quality; 2020: 1145 pages. Accessed September 25, 2023. Available at https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/cer-224-depression-children-final-report.pdf

138. Cortese S, Besag FM, Clark B, et al. Common practical questions - and answers - at the British Association for Psychopharmacology child and adolescent psychopharmacology course. *J Psychopharmacol*. 2023;37(2):119-134. doi:10.1177/02698811221140005

139. Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2022;79(4):300-312. doi:10.1001/jamapsychiatry.2021.4313

140. Gałecki P, Bliźniewska-Kowalska K. Treatment-resistant depression - recommendations of the National Consultant in the field of psychiatry. *Psychiatr Pol*. 2021;55(1):7-21. doi:10.12740/PP/OnlineFirst/115208

141. Shamseddeen W, Clarke G, Keller MB, et al. Adjunctive sleep medications and depression outcome in the treatment of serotonin-selective reuptake inhibitor resistant depression in adolescents study. *J Child Adolesc Psychopharmacol*. 2012;22(1):29-36. doi:10.1089/cap.2011.0027

142. Brent DA, Birmaher B. Treatment-resistant depression in adolescents: recognition and management. *Child and adolescent psychiatric clinics of North America*. 2006;15(4):1015-1034.

143. Braithwaite R. RE: A case of treatment-resistant depression in an older adult and a discussion of treatment options. *BJPsych Bull*. 2023;47(3):182-183. doi:10.1192/bjb.2023.21

144. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243-1252. doi:10.1056/NEJMoa052964

145. Maalouf FT, Atwi M, Brent DA. Treatment-resistant depression in adolescents: review and updates on clinical management. *Depression and anxiety*. 2011;28(11):946-954. doi:https://dx.doi.org/10.1002/da.20884

146. Glod CA, Lynch A, Flynn E, Berkowitz C, Baldessarini RJ. Open trial of bupropion SR in adolescent major depression. *J Child Adolesc Psychiatr Nurs*. 2003;16(3):123-130. doi:10.1111/j.1744-6171.2003.00123.x

147. Daviss WB, Bentivoglio P, Racusin R, Brown KM, Bostic JQ, Wiley L. Bupropion sustained release in adolescents with comorbid attention-deficit/hyperactivity disorder and depression. *J Am Acad Child Adolesc Psychiatry*. 2001;40(3):307-314. doi:10.1097/00004583-200103000-00010

148. Ayvaci ER, Croarkin PE. Special Populations: Treatment-Resistant Depression in Children and Adolescents. *The Psychiatric clinics of North America*. 2023;46(2):359-370. doi:https://dx.doi.org/10.1016/j.psc.2023.02.007

149. Ryan K, Hosanagar A. Ketamine Use in Child and Adolescent Psychiatry: Emerging Data in Treatment-Resistant Depression, Insights from Adults, and Future Directions. *Current psychiatry reports*. 2023;25(8):337-344. doi:https://dx.doi.org/10.1007/s11920-023-01432-w

150. Janssen Research & Development LLC. Study to Evaluate the Efficacy and Safety of 3 Fixed Doses of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Particpants Assessed to be at Imminent Risk for Suicide. NCT03185819. ClinicalTrials.gov; 2017. Last Updated May 3, 2023. Accessed October 25, 2023. Available at https://classic.clinicaltrials.gov/ct2/show/NCT03185819

151. Dwyer JB, Landeros-Weisenberger A, Johnson JA, et al. Efficacy of Intravenous Ketamine in Adolescent Treatment-Resistant Depression: A Randomized Midazolam-Controlled Trial. *Am J Psychiatry*. 2021;178(4):352-362. doi:10.1176/appi.ajp.2020.20010018

152. Cullen KR, Amatya P, Roback MG, et al. Intravenous Ketamine for Adolescents with Treatment-Resistant Depression: An Open-Label Study. *J Child Adolesc Psychopharmacol*. 2018;28(7):437-444. doi:10.1089/cap.2018.0030

153. Cullen KR, Amatya P, Roback MG, et al. Supplement to: Intravenous Ketamine for Adolescents with Treatment-Resistant Depression: An Open-Label Study *Journal of Child and Adolescent Psychopharmacology*. 2018;28(7):1-2. doi:http://doi.org/10.1089/cap.2018.0030

154. Kim S, Rush BS, Rice TR. A systematic review of therapeutic ketamine use in children and adolescents with treatment-resistant mood disorders. *European child & adolescent psychiatry*. 2021;30(10):1485-1501. doi:https://dx.doi.org/10.1007/s00787-020-01542-3

155. Weber G, Yao J, Binns S, Namkoong S. Case Report of Subanesthetic Intravenous Ketamine Infusion for the Treatment of Neuropathic Pain and Depression with Suicidal Features in a Pediatric Patient. *Case Rep Anesthesiol*. 2018;2018:9375910. doi:10.1155/2018/9375910

156. Di Vincenzo JD, Siegel A, Lipsitz O, et al. The effectiveness, safety and tolerability of ketamine for depression in adolescents and older adults: A systematic review. *Journal of psychiatric research*. 2021;137:232-241. doi:https://dx.doi.org/10.1016/j.jpsychires.2021.02.058

157. Taylor DM, Barnes TRE, Young AH. Chapter 3. Depression and anxiety disorders. *The Maudsley Prescribing Guidelines in Psychiatry*. 14th ed. John Wiley & Sons, Inc. ; 2021.

158. National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual. Process and methods [PMG20]. 2023. Last Updated November 21, 2023. Accessed November 29, 2023. Available at https://www.nice.org.uk/process/pmg20/chapter/writing-the-guideline#wording-the-recommendations

159. GLAD-PC Project Team. *Guidelines for Adolescent Depression in Primary Care (GLAD-PC) Toolkit*. The REACH Institute; 2018: 192 pages. Accessed Octobter 2, 2023. Available at http://www.gladpc.org/

160. Klein B, Rajendram R, Hrycko S, et al. Anxiety in children and youth: Part 1-Diagnosis. *Paediatrics & child health*. 2023;28(1):37-51. doi:https://dx.doi.org/10.1093/pch/pxac102

161. Bai S, Rolon-Arroyo B, Walkup JT, et al. Anxiety symptom trajectories from treatment to 5- to 12-year follow-up across childhood and adolescence. *Journal of child psychology and psychiatry, and allied disciplines*. 2023;64(9):1336-1345. doi:https://dx.doi.org/10.1111/jcpp.13796

162. Doyle MM. Anxiety Disorders in Children. *Pediatrics in review*. 2022;43(11):618-630. doi:https://dx.doi.org/10.1542/pir.2020-001198

163. Bobbitt S, Kawamura A, Saunders N, Monga S, Penner M, Andrews D. Anxiety in children and youth: Part 2-The management of anxiety disorders. *Paediatrics & child health*. 2023;28(1):52-66. doi:https://dx.doi.org/10.1093/pch/pxac104

164. Bandelow B, Allgulander C, Baldwin DS, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders - Version 3. Part I: Anxiety disorders. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2023;24(2):79-117. doi:https://dx.doi.org/10.1080/15622975.2022.2086295

165. Andrews G, Bell C, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. *Australian & New Zealand Journal of Psychiatry*. 2018;52(12):1109-1172. doi:10.1177/0004867418799453

166. Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry*. 2001;158(12):2008-2014. doi:10.1176/appi.ajp.158.12.2008

167. Walkup JT, Labellarte MJ, Riddle MA, et al. Fluvoxamine for the Treatment of Anxiety Disorders in Children and Adolescents. *New England Journal of Medicine*. 2001;344(17):1279-1285. doi:10.1056/NEJM200104263441703

168. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med*. 2008;359(26):2753-2766. doi:10.1056/NEJMoa0804633

169. Strawn JR, Mills JA, Schroeder H, et al. Escitalopram in Adolescents With Generalized Anxiety Disorder: A Double-Blind, Randomized, Placebo-Controlled Study. *J Clin Psychiatry*. 2020;81(5)doi:10.4088/JCP.20m13396

170. Birmaher B, Axelson DA, Monk K, et al. Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2003;42(4):415-423. doi:10.1097/01.Chi.0000037049.04952.9f

171. Beidel DC, Turner SM, Sallee FR, Ammerman RT, Crosby LA, Pathak S. SET-C versus fluoxetine in the treatment of childhood social phobia. *J Am Acad Child Adolesc Psychiatry*. 2007;46(12):1622-1632. doi:10.1097/chi.0b013e318154bb57

172. Wagner KD, Berard R, Stein MB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry*. 2004;61(11):1153-1162. doi:10.1001/archpsyc.61.11.1153

173. Strawn JR, Prakash A, Zhang Q, et al. A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(4):283-293. doi:10.1016/j.jaac.2015.01.008

174. March JS, Entusah AR, Rynn M, Albano AM, Tourian KA. A Randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biol Psychiatry*. 2007;62(10):1149-1154. doi:10.1016/j.biopsych.2007.02.025

175. Rynn MA, Riddle MA, Yeung PP, Kunz NR. Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *Am J Psychiatry*. 2007;164(2):290-300. doi:10.1176/ajp.2007.164.2.290

176. American Psychiatric Association. Obsessive-Compulsive and Related Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition, Text Revision ed. American Psychiatric Association; 2022. Accessed October 16, 2023

177. Avasthi A, Sharma A, Grover S. Clinical Practice Guidelines for the Management of Obsessive-Compulsive Disorder in Children and Adolescents. *Indian journal of psychiatry*. 2019;61(Suppl 2):306-316. doi:https://dx.doi.org/10.4103/psychiatry.IndianJPsychiatry_554_18

178. Bandelow B, Allgulander C, Baldwin DS, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders - Version 3. Part II: OCD and PTSD. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2023;24(2):118-134. doi:https://dx.doi.org/10.1080/15622975.2022.2086296

179. Fung R, Elbe D, Stewart SE. Retrospective Review of Fluvoxamine-Clomipramine Combination Therapy in Obsessive-Compulsive Disorder in Children and Adolescents. *J Can Acad Child Adolesc Psychiatry*. 2021;30(3):150-155.

180. Reinblatt SP, Walkup JT. Psychopharmacologic treatment of pediatric anxiety disorders. *Child and adolescent psychiatric clinics of North America*. 2005;14(4):877-908.

181. Stewart SE, Hezel D, Stachon AC. Assessment and medication management of paediatric obsessive-compulsive disorder. *Drugs*. 2012;72(7):881-893. doi:https://dx.doi.org/10.2165/11632860-000000000-00000

182. Bloch MH, Storch EA. Assessment and management of treatment-refractory obsessive-compulsive disorder in children. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2015;54(4):251-262. doi:https://dx.doi.org/10.1016/j.jaac.2015.01.011

183. Simeon JG, Thatte S, Wiggins D. Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. *Psychopharmacol Bull*. 1990;26(3):285-290. https://www.ncbi.nlm.nih.gov/pubmed/2274627

184. Figueroa Y, Rosenberg DR, Birmaher B, Keshavan MS. Combination treatment with clomipramine and selective serotonin reuptake inhibitors for obsessive-compulsive disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 1998;8(1):61-67. doi:10.1089/cap.1998.8.61 https://www.ncbi.nlm.nih.gov/pubmed/9639080

185. Pallanti S, Quercioli L, Paiva RS, Koran LM. Citalopram for treatment-resistant obsessive-compulsive disorder. *Eur Psychiatry*. 1999;14(2):101-106. doi:10.1016/s0924-9338(99)80725-1

186. Marazziti D, Golia F, Consoli G, et al. Effectiveness of long-term augmentation with citalopram to clomipramine in treatment-resistant OCD patients. *CNS Spectr*. 2008;13(11):971-976. doi:10.1017/s1092852900014024

187. Diniz JB, Shavitt RG, Pereira CA, et al. Quetiapine versus clomipramine in the augmentation of selective serotonin reuptake inhibitors for the treatment of obsessive-compulsive disorder: a randomized, open-label trial. *J Psychopharmacol*. 2010;24(3):297-307. doi:10.1177/0269881108099423

188. Riddle MA, Reeve EA, Yaryura-Tobias JA, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(2):222-229. doi:10.1097/00004583-200102000-00017

189. Geller DA, Hoog SL, Heiligenstein JH, et al. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(7):773-779. doi:10.1097/00004583-200107000-00011

190. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(12):1431-1438. doi:10.1097/00004583-200212000-00014

191. Riddle MA, Scahill L, King RA, et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 1992;31(6):1062-1069. doi:10.1097/00004583-199211000-00011

192. Alaghband-Rad J, Hakimshooshtary M. A randomized controlled clinical trial of citalopram versus fluoxetine in children and adolescents with obsessive-compulsive disorder (OCD). *Eur Child Adolesc Psychiatry*. 2009;18(3):131-135. doi:10.1007/s00787-007-0634-z

193. March JS, Biederman J, Wolkow R, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *Jama*. 1998;280(20):1752-1756. doi:10.1001/jama.280.20.1752

194. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *Jama*. 2004;292(16):1969-1976. doi:10.1001/jama.292.16.1969

195. Asbahr FR, Castillo AR, Ito LM, Latorre MR, Moreira MN, Lotufo-Neto F. Group cognitive-behavioral therapy versus sertraline for the treatment of children and adolescents with

obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1128-1136. doi:10.1097/01.chi.0000177324.40005.6f

196. Geller DA, Wagner KD, Emslie G, et al. Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2004;43(11):1387-1396. doi:10.1097/01.chi.0000138356.29099.f1

197. Leonard HL, Swedo SE, Rapoport JL, et al. Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents. A double-blind crossover comparison. *Arch Gen Psychiatry*. 1989;46(12):1088-1092. doi:10.1001/archpsyc.1989.01810120030006

198. Flament MF, Rapoport JL, Berg CJ, et al. Clomipramine treatment of childhood obsessive-compulsive disorder. A double-blind controlled study. *Arch Gen Psychiatry*. 1985;42(10):977-983. doi:10.1001/archpsyc.1985.01790330057007

199. Scheeringa MS. PTSD in Children Younger Than the Age of 13: Toward Developmentally Sensitive Assessment and Management. *J Child Adolesc Trauma*. 2011;41(3):181-197. doi:10.1080/19361521.2011.597079

200. Cohen JA, Bukstein O, Walter H, et al. Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. *J Am Acad Child Adolesc Psychiatry*. 2010;49(4):414-430.

201. Lee L. *PTSD and Aging*. PTSD NCf; 2019: 15 pages. Accessed October 26, 2023. Available at https://www.ptsd.va.gov/publications/rq_docs/V30N4.pdf

202. Hamblen J, Barnett E. PTSD in Children and Adolescents. 2022. Last Updated October 6, 2022. Accessed October 26, 2023. Available at https://www.ptsd.va.gov/professional/treat/specific/ptsd_child_teens.asp#one

203. Alisic E, Zalta AK, van Wesel F, et al. Rates of post-traumatic stress disorder in trauma-exposed children and adolescents: meta-analysis. *Br J Psychiatry*. 2014;204:335-340. doi:10.1192/bjp.bp.113.131227

204. Phoenix Australia. *Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Postraumatic Stress Disorder and Complex PTSD. Chapter 6 Treatment Recommendations*. Phoenix Australia; 2021: 17 pages. Last Updated December 2021. Accessed October 2, 2023. Available at https://www.phoenixaustralia.org/wp-content/uploads/2022/11/PTSD-Guidelines-Chapter-6-Treatment-recommendations.pdf

205. National Institute for Health and Care Excellence (NICE). *Post-traumatic stress disorder*. 2018: 54 pages. Last Updated December 5, 2018. Available at https://www.nice.org.uk/guidance/ng116/resources/posttraumatic-stress-disorder-pdf-66141601777861

206. ISTSS Guidelines Committee. *Posttraumatic Stress Disorder Prevention and Treatment Guidelines. Methodology and Recommendations*. Internatioanl Society for Traumatic Stress Studies (ISTSS); 2019: 29 pages. Accessed October 3, 2023. Available at

https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_PreventionTreatmentGuidelines_FNL-March-19-2019.pdf.aspx

207. Walton JL, Cuccurullo LJ, Raines AM, et al. Sometimes Less is More: Establishing the Core Symptoms of PTSD. *J Trauma Stress*. 2017;30(3):254-258. doi:10.1002/jts.22185

208. Robb AS, Cueva JE, Sporn J, Yang R, Vanderburg DG. Sertraline treatment of children and adolescents with posttraumatic stress disorder: a double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2010;20(6):463-471. doi:10.1089/cap.2009.0115

209. Cohen JA, Mannarino AP, Perel JM, Staron V. A pilot randomized controlled trial of combined trauma-focused CBT and sertraline for childhood PTSD symptoms. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):811-819. doi:10.1097/chi.0b013e3180547105

210. Phoenix Australia. *Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder and Complex PTSD. Chapter 3 General Considerations When Working with Children and Adolescents* Phoenix Australia; 2021: 30 pages. Accessed October 2, 2023. Available at https://www.phoenixaustralia.org/wp-content/uploads/2022/07/UPDATED-Chapter-3-Children-and-adolescents.pdf

211. Meyers RS, Thackray J, Matson KL, et al. Key Potentially Inappropriate Drugs in Pediatrics: The KIDs List. *J Pediatr Pharmacol Ther*. 2020;25(3):175-191. doi:10.5863/1551-6776-25.3.175

212. Royal College of Psychiatrists' Psychopharmacology Committee. *Use of monoamine oxidase inhibitors in psychiatric practice*. PS03/20. Royal College of Psychiatrists; 2020: 10 pages. Accessed September 25, 2023. Available at https://www.bap.org.uk/pdfs/PS03-20-July2020.pdf

213. Anonymous. Practice parameters for the assessment and treatment of children and adolescents with depressive disorders. AACAP. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1998;37(10 Suppl):63S-83S.

214. Wyeth Pharmaceuticals LLC. Desvenlafaine Succinate. Micromedex DRUGDEX. Micromedexsolutions.com; 2023. Last Updated September 20, 2023. Accessed October 6, 2023. Available at https://www.micromedexsolutions.com

215. ZURZUVAE (zuranolone) capsules, for oral use [controlled substance schedule pending]. Package Insert. Sage Therapeutics I; 2023. Accessed October 3, 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217369Orig2s000Corrected_lbl.pdf

216. Curry SJ, Krist AH, Owens DK, et al. Interventions to Prevent Perinatal Depression: US Preventive Services Task Force Recommendation Statement. *Jama*. 2019;321(6):580-587. doi:10.1001/jama.2019.0007

217. Malaysian Health Technology Assessment Section. *Management of Major Depressive Disorder, Second Edition*. Ministry of Health Malaysia; 2019: 83 pages. Accessed October 3, 2023. Available at https://www.moh.gov.my/moh/resources/Penerbitan/CPG/1)_CPG_Management_Major_Depressive_Disorder_(Second_Edition).pdf

218. European AIDS Clinical Society (EACS). *Guidelines Version 11.1*. 2022: 151 pages. Last Updated October 2022. Accessed October 23, 2023. Available at https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf

219. Bennabi D, Yrondi A, Charpeaud T, et al. Clinical guidelines for the management of depression with specific comorbid psychiatric conditions French recommendations from experts (the French Association for Biological Psychiatry and Neuropsychopharmacology and the fondation FondaMental). *BMC Psychiatry*. 2019;19(1):50. doi:10.1186/s12888-019-2025-7

220. 2020 Recommendations for Preventive Pediatric Health Care. *Pediatrics*. 2020;145(3)doi:10.1542/peds.2020-0013

221. Pfeiffer HCV, Wickstrom R, Skov L, et al. Clinical guidance for diagnosis and management of suspected Pediatric Acute-onset Neuropsychiatric Syndrome in the Nordic countries. *Acta paediatrica (Oslo, Norway : 1992)*. 2021;110(12):3153-3160. doi:https://dx.doi.org/10.1111/apa.15875

APPENDIX A – LIST OF ANTIDEPRESSANTS BY ACTIVE INGREDIENT

Overall, we identified 36 unique active ingredients with pharmacologic category of "antidepressant" per the drug compendia Lexicomp, as shown below in **Table A1**.

Table A1. Active Ingredients Classified by Lexicomp as an Antidepressant, by Drug Class[a,b]

SSRI	SNRI
• Citalopram[71] • Escitalopram[81] • Fluoxetine[79] • Fluvoxamine[66] • Paroxetine[82] • Sertraline[67] • Vilazodone[87,c] • Vortioxetine[89,d]	• Desvenlafaxine[96] • Duloxetine[98] • Levomilnacipran[99] • Milnacipran[101] • Venlafaxine[69]
Alpha-2 antagonist	**Dopamine-/ norepinephrine-reuptake inhibitor**
• Mirtazapine[116]	• Bupropion[43]
Serotonin reuptake inhibitor/antagonist[d]	**Tricyclic (tertiary amine)**
• Trazodone[83] • Nefazodone[118]	• Amitriptyline[85] • Clomipramine[91] • Doxepin[74] • Imipramine[73] • Trimipramine[93]
Tricyclic (secondary amine)	**Monoamine oxidase inhibitor**
• Amoxapine[105e] • Desipramine[72] • Nortriptyline[75] • Protriptyline[92]	• Isocarboxazid[107] • Phenelzine[108] • Selegiline[76] • Tranylcypromine[110]
GABA A receptor positive modulator	**NMDA receptor antagonist**
• Brexanolone[41] • Zuranolone[42]	• Esketamine[40] • Ketamine[39,f] • Dextromethorphan (when co-formulated with bupropion)[52,g]
Serotonin 5-HT1A Receptor Agonist	
• Gepirone[114]	

Abbreviations: GABA, Gamma-aminobutyric acid; NMDA, N-Methyl-D-Aspartate; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; US, United States of America

[a] Active ingredients are listed by Lexicomp antidepressant categories, which incorporates pharmacologic mechanism.

[b] Only antidepressants still commercially available in the US in at least 1 formulation were considered. For example, the antidepressant maprotiline has been discontinued in the US, so it was not considered.

[c] Vilazodone may also be classified as a serotonin partial agonist (with high affinity for 5-HT_{1A} receptors[87]) and serotonin reuptake inhibitor[128]

[d] Vortioxetine may also be classified as a serotonin reuptake inhibitor and serotonin receptor antagonist or serotonin modulator,[128] like trazodone and nefazodone

[e] Also classified as a serotonin-norepinephrine reuptake inhibitor and serotonin receptor antagonist[128]

[f] Classified only as "antidepressant"(and "general anesthetic") by Lexicomp

[g] Classified as an NDMA antagonist by Lexicomp, but included here since it is indicated for MDD

Table A2. Unique Antidepressant Dosage Forms by Active Ingredient and/or Brand Name[a]

SSRIs	SNRIs	TCAs	MAOIs	Other antidepressants
Citalopram[78] Generic: oral capsule (30 mg) Generic: oral solution (10 mg/5 mL) Generic/Celexa: oral tablet (10 mg, 20 mg, 40 mg)	**Desvenlafaxine[97]** Generic: oral tablet, ER (50 mg, 100 mg) **Desvenlafaxine succinate[214]** Generic/Pristiq: oral tablet, ER (25 mg, 50 mg, 100 mg)	**Amitriptyline hydrochloride[56]** Generic: oral tablet (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg) Elavil: oral tablet (25 mg) **Amitriptyline hydrochloride/perphenazine[49]** Generic: oral tablet (10 mg/2mg, 10 mg/4 mg, 25 mg/2 mg, 25 mg/4 mg, 50 mg/4 mg) **Amitriptyline hydrochloride/chlordiazepoxide[50]** Generic: oral tablet (12.5 mg/5 mg, 25 mg/10 mg)	**Isocarboxazid[61]** Marplan: oral tablet (10 mg)	**Brexanolone[62]** Zulresso: intravenous solution (5 mg/1mL)
Escitalopram[55] Generic: oral solution (5 mg/mL, 1 mg/mL) Generic/Lexapro: oral tablet (5 mg, 10 mg, 20 mg)	**Duloxetine[63]** Generic/Cymbalta/Drizalma Sprinkle: oral capsule, DR (20 mg, 30 mg, 40 mg [not Cymbalta], 60 mg) Irenka: oral capsule, DR (40 mg)	**Amoxapine[106]** Generic: oral tablet (25 mg, 50 mg, 100 mg, 150 mg)	**Phenelzine[77]** Generic/Nardil: oral tablet (15 mg)	**Bupropion hydrobromide[46]** Aplenzin: oral tablet, ER 24 hr (174 mg, 348 mg, 522 mg) **Bupropion hydrochloride[45]** Generic: oral tablet (75 mg, 100 mg) Generic: oral tablet, ER (150 mg) Generic: oral tablet, ER 12 hr (100 mg, 150 mg, 200 mg) Generic: oral tablet, ER 24 hr (150 mg, 300 mg, 450 mg) Wellbutrin XL: oral tablet, ER 24 hr (150 mg, 300 mg) Forfivo XL: oral tablet, ER 24 hr (450 mg) Wellbutrin SR: oral tablet, ER 12 hr (100 mg, 150 mg, 200 mg) Wellbutrin: oral tablet (100 mg) **Bupropion hydrochloride/dextromethorphan hydrobromide[111]** Auvelity: oral tablet, ER (105 mg/45 mg)
Fluoxetine[51] Generic/Prozac: oral capsule (10 mg, 20 mg, 40 mg) Generic: oral capsule, DR (90 mg) Generic: oral solution or syrup (20 mg/5 mL) Generic: oral tablet (10 mg, 20 mg, 60 mg) **Fluoxetine hydrochloride-olanzapine[51]** Generic/Symbyax: oral capsule (25 mg-3 mg, 25 mg-6 mg, 50 mg-6 mg, 50 mg-12 mg)	**Levomilnacipran hydrochloride[100]** Fetzima: oral capsule, ER (20 mg, 40 mg, 80 mg, 120 mg)	**Clomipramine[65]** Generic/Anafranil: oral capsule (25 mg, 50 mg, 75 mg)	**Selegiline[94]** Emsam: transdermal patch, ER (6 mg/24 hr, 9 mg/24hr, 12 mg/24 hr) **Selegiline hydrochloride[109]** Generic/Eldepryl: oral capsule (5 mg) Generic: oral tablet (5 mg) Zelapar: oral tablet, dist (1.25 mg)	**Esketamine[112]** Spravato: nasal spray (28 mg/0.2 mL) **Gepirone[115]** Exxua: oral tablet, ER (18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg) **Ketamine[54]** Ketalar/generic: solution for injection (10 mg/1mL, 50 mg/1 mL, 100 mg/1 mL) Generic: intravenous solution (50 mg/1 mL) **Mirtazapine[117]** Generic: oral tablet (7.5 mg, 15 mg, 30 mg, 45 mg) Generic/Remeron Soltab: oral tablet, dist (15 mg, 30 mg, 45 mg) Remeron: oral tablet (15 mg, 30 mg)

Table A2. Unique Antidepressant Dosage Forms by Active Ingredient and/or Brand Name[a]

SSRIs	SNRIs	TCAs	MAOIs	Other antidepressants
Fluvoxamine[64] Generic: oral capsule, ER (100 mg, 150 mg) Generic: oral tablet (25 mg, 50 mg, 100 mg)	**Milnacipran**[102] Savella: oral tablet (12.5 mg, 25 mg, 50 mg, 100 mg)	**Desipramine**[84] Generic: oral tablet (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg)	**Tranylcypromine**[70] Generic/Parnate: 10 mg	**Nefazodone**[119] Generic: oral tablet (50 mg, 100 mg, 150 mg, 200 mg, 250 mg)
				Trazodone[120] Generic: oral tablet (50 mg, 100 mg, 150 mg, 300 mg)
Paroxetine hydrochloride[80] Generic/Paxil: oral suspension (10 mg/5 mL) Generic/Paxil: oral tablet (10 mg, 20 mg, 30 mg, 40mg) Generic/Paxil CR: oral tablet, ER (12.5 mg, 25 mg, 37.5 mg) **Paroxetine mesylate**[95] Generic/Brisdelle: oral capsule (7.5 mg)	**Venlafaxine hydrochloride**[68] Generic/Effexor XR: oral capsule, ER (37.5 mg, 75 mg, 150 mg) Generic: oral tablet, ER (37.5 mg, 75 mg, 150 mg, 225 mg) Generic: oral tablet (25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg)	**Doxepin**[57] Generic: oral capsule (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg) Generic: oral solution (10 mg/1 mL) Generic/Silenor: oral tablet (3 mg, 6 mg) Generic/Prudoxin/Zonalon: topical cream (5%)		**Zuranolone**[215] Zurzuvae: oral capsule (20 mg, 25 mg, 30 mg)
Sertraline[53] Generic: oral capsule (150 mg, 200 mg) Generic/Zoloft: oral solution (20 mg/1 mL) Generic: oral tablet (25 mg, 50 mg, 100 mg)		**Imipramine hydrochloride**[48] Generic: oral tablet (10 mg, 25 mg, 50 mg) **Imipramine pamoate**[47] Generic: oral capsule (75 mg, 100 mg, 125 mg, 150 mg)		
Vortioxetine[90] Trintellix: oral tablet (5 mg, 10 mg, 20 mg)		**Nortriptyline**[58] Generic/Pamelor: oral capsule (10 mg, 25 mg, 50 mg, 75 mg) Generic: oral solution (10 mg/5 mL)		
Vilazodone[88] Generic/Viibryd: oral tablet (10 mg, 20 mg, 40 mg)		**Protriptyline**[59] Generic: oral tablet (5 mg, 10 mg)		
		Trimipramine[60] Generic: oral capsule (25 mg, 50 mg, 100 mg)		

[a] *Information is per the drug compendia, Micromedex, except for zuranolone and gepirone, whose information is per the respective prescribing information because updated information was not yet available in Micromedex.*

Abbreviations: CR, controlled release; DR, delayed release; ER, extended release; mg, milligram; mL, milliliter; MAOI, monoamine-oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant;

APPENDIX B – LITERATURE SEARCHES

Clinical Practice Guideline Search (2018-present)

Table B1. Ovid-Medline Literature Search Strategy for Pediatric Depressive or Anxiety Disorders, Obsessive Compulsive Disorder, or PTSD Treatment Guidelines

Ovid-Medline Session Results

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to September 11, 2023

Date of search: September 12, 2023

#	Searches	Results
1	exp depression/ or exp Depressive Disorder/ or *affective symptoms/	264881
2	(((mood or mental or behavior* or dysphoric) adj2 disorder*) or (depressed or depressive? or depression or MDD or TRD or dysthymi*) or (affective adj2 (state* or symptom* or disorder*))).ti.	206694
3	Anxiety/ or exp Anxiety Disorders/ or mutism/	185472
4	(anxiet* or anxious or (affective adj (symptom* or disorder*)) or adjustment disorder* or (agoraphobi* or phobic or phobia* or panic or obsessive or OCD or stress or neurosis or neuroses or neurotic or GAD or psychoneuro* or acrophobi* or claustrophobi* or neophobi* or Ophidiophobi* or mutism*)).ti.	398473
5	PTSD.ti,ab,kw,kf. or ((stress adj2 (syndrome or disorder)) or PTSS).ti.	48528
6	1 or 2 or 3 or 4 or 5	766309
7	exp child/ or adolescent/ or minors/	3376660
8	(children* or child or childhood or teen* or paediatr* or pediatr* or adolescen* or boy* or girl* or youth* or minors or juvenile or school-aged).ti,ab,kw.	2251771
9	7 or 8	4089891
10	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or treatment guidelines/ or Clinical Decision Rules/	430013
11	(guideline or practice guideline or consensus development conference).pt.	47536
12	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf.	47142
13	(standards or guideline or guidelines).ti,kf. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf. or consensus*.ab. /freq=2	235078
14	(guideline* or standards or consensus* or recommendat*).au.	10
15	10 or 11 or 12 or 13 or 14	607330
16	6 and 9 and 15	1447
17	limit 16 to yr="2018 -Current"	**397**

Epistemonikos search performed September 12, 2023

Table B2. Epistemonikos Literature Search Strategy for Pediatric Depressive or Anxiety Disorders, Obsessive Compulsive Disorder, or PTSD Treatment Guidelines

Database(s): Epistemonikos Session Results
Date of search: September 12, 2023

#	Searches	Results
1	(((mood OR mental OR behavior* OR affective OR dysphor*) AND disorder*) OR (depressed OR depression OR MDD OR TRD OR dysthymi*) OR (anxiet* OR agoraphobi* OR phobic OR phobia* OR panic OR obsessive OR OCD OR stress OR neurosis OR neuroses OR neurotic OR GAD OR psychoneuro* OR acrophobi* OR claustrophobi* OR neophobi* OR Ophidiophobi* OR mutism*) OR (posttrauma* OR PTSD OR PTSS)) [Title or Abstract]	246,169
2	**AND** (children* OR child OR childhood OR teen* OR paediatr* OR pediatr* OR adolescen* OR boy* OR girl* OR youth* OR minors OR juvenile OR school-aged) [Title or Abstract]	37,218
3	**AND** ((practice guideline) OR (guidance OR guideline*) OR consensus OR (position statement*)) [Title]	130
4	From 2018 – 2023	**80**

Pediatric Multiple Antidepressant Supplemental Search

Table B3. Ovid-Medline Literature Search Strategy for Reviews or Expert Opinion Articles about Use of Multiple Antidepressants

Ovid-Medline Session Results
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to October 17, 2023
Date of search: October 18, 2023

#	Searches	Results
1	(children* or child or childhood or teen* or paediatr* or pediatr* or adolescen* or boy* or girl* or youth* or minors or juvenile or school-aged).ti,ab.	2229472
2	exp child/ or adolescent/ or minors/	3382511
3	1 or 2	4092796
4	*Retreatment/ or *Drug Therapy, Combination/ or *Polypharmacy/	8358
5	(citalopram or escitalopram or fluoxetin* or fluvoxamin* or paroxetin* or sertralin* or Vortioxetin* or vilazodon* or desvenlafax* or duloxetin* or levomilnacip* or venlafaxine* or mirtazapin* or bupropion or trazodon* or nefazodon* or amitriptylin* or clomipramin* or doxepin* or imipramin* or trimipramin* or amoxapin* or desipramin* or nortriptylin* or protriptylin* or isocarboxazid* or moclobemid* or phenelzin* or selegilin* or tranylcypromin* or brexanolon* or zuranolon* or gepiron* or esketamin* or ketamin* or (dextromethorphan and bupropion)).ti,ab.	89000
6	exp antidepressive agents/ or anti-anxiety agents/ or Adrenergic Uptake Inhibitors/ or "Serotonin and Noradrenaline Reuptake Inhibitors"/ or Selective Serotonin	193679

Table B3. Ovid-Medline Literature Search Strategy for Reviews or Expert Opinion Articles about Use of Multiple Antidepressants

Ovid-Medline Session Results

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to October 17, 2023

Date of search: October 18, 2023

#	Searches	Results
	Reuptake Inhibitors/ or Adrenergic alpha-2 Receptor Antagonists/ or Monoamine Oxidase Inhibitors/ or gaba modulators/	
7	Citalopram/ or Escitalopram/ or Fluoxetine/ or Fluvoxamine/ or paroxetine/ or sertraline/ or vortioxetine/ or vilazodone hydrochloride/ or desvenlafaxine succinate/ or duloxetine hydrochloride/ or levomilnacipran/ or milnacipran/ or venlafaxine hydrochloride/ or mirtazapine/ or bupropion/ or trazodone/ or amitriptyline/ or clomipramine/ or doxepin/ or imipramine/ or trimipramine/ or amoxapine/ or desipramine/ or nortriptyline/ or protriptyline/ or isocarboxazid/ or moclobemine/ or phenelzine/ or selegiline/ or tranylcypromine/ or ketamine/	74056
8	(anti-depress* or antidepress* or anti-anxiet* or antianxiet* or anxioly*).ti,ab.	94082
9	5 or 6 or 7 or 8	265233
10	4 and 9	372
11	((anti-depress* or antidepress* or anti-anxiet* or antianxiet* or anxioly*) adj2 (augment* or enhancement or add-on* or addition* or supplement* or cotreatment* or co-treatment* or adjunctive* or concurrent* or concomitant* or simultaneous* or parallel* or polypharmacy or combin*)).ti,ab.	2702
12	((treatment-resistant or non-respons* or non-improv* or treatment-refractor*) adj3 (anxiet* or PTSD or OCD or post-traumatic or obsessive-compulsive)).ti,ab.	746
13	((treatment-resistant or non-respons* or non-improv* or treatment-refractor*) adj3 (MDD or depression*)).ti,ab.	4326
14	limit 13 to yr="2014 -Current"	3025
15	12 or 14	3708
16	(treatment-resistant or treatment-refractor*).ti,ab.	15442
17	exp anxiety disorders/ or exp stress disorders, traumatic/	134190
18	exp depressive disorder/	122666
19	limit 18 to yr="2014 -Current"	39870
20	17 or 19	168036
21	16 and 20	2886
22	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	544354
23	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	510078
24	"review".pt. or (expert adj2 opinion*).ti,ab. or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf. or algorithms/	3584494
25	3584494	3881846
26	10 or 11 or 15 or 21	7159

Table B3. Ovid-Medline Literature Search Strategy for Reviews or Expert Opinion Articles about Use of Multiple Antidepressants

Ovid-Medline Session Results

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to October 17, 2023

Date of search: October 18, 2023

#	Searches	Results
27	3 and 25 and 26	**135**

Table B4. Epistemonikos Literature Search Strategy for Reviews or Expert Opinion Articles about Use of Multiple Antidepressants

Database(s): Epistemonikos Session Results

Date of search: October 18, 2023

#	Searches	Results
Search 1		
1	(anti-depress* OR antidepress* OR anti-anxiet* OR antianxiet* OR anxioly*) [Title or Abstract]	20,876
2	**AND** (augment* OR polypharm* OR combin*) [Title or Abstract]	389,588
3	**AND** (child* OR teen* OR paediatr* OR paediatr* OR pediatr* OR youth* OR adolescen*) [Title or Abstract]	394,078
4	Limited to "Systematic Reviews," "Broad Synthesis," or "Structured Summary" results	**117**
Search 2		
1	(treatment-resistan* OR treatment-refractor*) [Title or Abstract]	3,714
2	(anxiet* OR PTSD OR OCD OR MDD OR depression* OR post-traumatic OR obsessive-compulsive) [Title or Abstract]	162,867
3	(child* OR teen* OR paediatr* OR paediatr* OR pediatr* OR youth* OR adolescen*) [Title or Abstract]	394,078
4	Limited to "Systematic Reviews," "Broad Synthesis," or "Structured Summary" results	**30**

APPENDIX C – EXCLUDED REVIEWED GUIDELINES

We screened 60 full-text publications identified from our literature search for guidelines. We reviewed guidelines for pediatric treatment recommendations regarding a) the indicated age for use of antidepressants, and b) any indications/scenarios for combined use of 1 or more antidepressants. Agents were considered antidepressants if they are categorized as "antidepressant" in Lexicomp (see **Appendix A** for the list of active ingredients considered antidepressants). The table below (Table C1) lists the guidelines or practice parameters that were **excluded** during the screening process, organized by mental health condition.

Table C1. Excluded Screened Clinical Practice Guidelines by Target Condition(s)

Unipolar Depression Guidelines

• Interventions to Prevent Perinatal Depression by the United States Preventative Services Task Force (2019)[216]
  ○ Excluded due to a focus on preventing perinatal depression. Of note, young motherhood (age <19) is a risk factor for developing perinatal depression.
• Management of Major Depressive Disorder, 2nd Addition by The Malaysian Health Technology Assessment Section (MaHTAS) (2019)[217]
  ○ Only addresses treatment of adults
• HIV and comorbidities guideline (version 11.1) by the European AIDS Clinical Society (EACS) (2022)[218]
  ○ This guideline provides some limited recommendations about the management of depression in people with HIV. Although the target age for recommendations is not stated, we inferred that treatment recommendations are for adults based on specific medications and doses recommended.

Anxiety Disorders Guidelines
• HIV and comorbidities guideline (version 11.1) by the European AIDS Clinical Society (EACS) (2022)[218]   ○ This guideline provides some limited recommendations about the management of anxiety in people with HIV. Although the target age for recommendations is not stated, we inferred that treatment recommendations are for adults based on specific medications and doses recommended.
Other/Multi-disorder Guidelines

• Use of monoamine oxidase inhibitors in psychiatric practice by the Royal College of Psychiatrists (2020)[212]
  ○ Scope of recommendations is specific to adults
• Clinical guidelines for the management of depression with specific comorbid psychiatric conditions. French recommendations from experts (the French Association for Biological Psychiatry and Neuropsychopharmacology and the foundation FondaMental) (2019)[219]
  ○ Although not well defined, we infer that antidepressant recommendations are for adults since it is said recommendations are "…complementary to the Formal Consensus Guidelines for treatment of adults with treatment-resistant depression (TRD)", and no cited references are specific to children, adolescents, or youth.
• 2020 Recommendations for Preventative Pediatric Health Care by the American Academy of Pediatrics (2020)[220]
  ○ Only an update to the policy statement, which does not include pediatric mental health recommendations
• Clinical guidance for diagnosis and management of suspected pediatric acute-onset neuropsychiatric syndrome in Nordic countries (2021) by multiple authors (consensus)[221]
  ○ This consensus statement primarily addresses the medical diagnosis and management of this condition.

APPENDIX D – ANTIDEPRESSANT FDA-APPROVED PEDIATRIC INDICATIONS, DOSING, AND LABELED CONTRAINDICATIONS

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram[78]				
Citalopram: oral capsule, oral tablet, oral solution	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age ≥ 6 years: 40 mg daily[b,c] **or** Age >13 years: 70 mg daily[78,d]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Concomitant use with pimozide due to QT prolongation risk
Escitalopram[55]				
Escitalopram: oral solution, oral tablets	• Major depressive disorder, age 12 or older • Generalized anxiety disorder, age 7 or older	• 10-20 mg daily • Age 7-11 years: 10-20mg daily • Age 12-17 years: 10-15 mg daily	Age 6-11 years:10-20 mg daily[b,c] Age ≥ 12 years: 30 mg daily[b] **or** Adolescents: 20 mg daily[c]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk
Fluoxetine[51]				
Fluoxetine: IR oral capsule, DR oral capsule, oral solution	• Major depressive disorder, age 8 or older • Obsessive compulsive disorder, age 7 or older	• 10-20 mg daily • 10-60 mg daily (dose range of 20-60 mg daily is recommended, despite little experience with doses > 20 mg)	Age ≥ 6 years: 60 mg daily[b] **or** Age 4-6 years: 5-10 mg daily[c] Age 6-12 years: 40 mg daily[c] Age ≥ 12 years: 60-80 mg daily[c]	• Concomitant use with an MAOI (wait at least 5 weeks since last fluoxetine dose to start MAOI; and wait at least 14 days after MAOI to start fluoxetine) due to serotonin syndrome risk. • Concomitant use with pimozide or thioridazine due to QT prolongation risk
Fluoxetine: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as above
Fluoxetine-**olanzapine**: oral capsule	• Bipolar disorder I depression, age 10 to 17 years	• Fluoxetine 25-50 mg-olanzapine 6-12 mg daily	Fluoxetine 50 mg-olanzapine 12 mg[c]	• Same as fluoxetine monotherapy
Fluvoxamine[64]				
Fluvoxamine: IR oral tablet	• Obsessive-compulsive disorder, age 8 or older	• Age 8-11 years: 50-200 mg daily • Age 12-17 years: 50-200 mg daily	Age 8-11 years: 200 mg daily[b] **or** Age 8 to 12 years: 150 mg daily[c] Age ≥ 12 years: 300 mg daily [b,c]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Concomitant use with alosetron, pimozide, thioridazine, tizanidine, or ramelteon due to QT prolongation risk
Fluvoxamine: ER oral capsule	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as IR capsule

[a] *Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.*

[b] *The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)*

[c] *Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*

[d] *The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources*

[e] *The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source*

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Paroxetine[80,95]				
Paroxetine HCl: oral suspension, IR oral tablet, ER oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Pre-adolescents: 40 mg daily[c] Adolescents: 60 mg daily[c]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Concomitant use with pimozide or thioridazine due to QT prolongation risk
Paroxetine mesylate: oral capsule	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as Paroxetine HCl
Sertraline[53]				
Sertraline HCl: oral capsule, oral concentrate, oral tablet	• Obsessive-compulsive disorder, age 6 or older	• Age 6-12 years: 25-200 mg daily • Age 13-17 years: 50-200 mg daily	Age 6-17 years: 200 mg daily[b] **or** Age 6-12 years: 150 mg daily[c] Adolescents: 200 mg daily[c]	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start sertraline, do not initiate an MAOI within 5 days of discontinuing sertraline) due to serotonin syndrome risk. • Concomitant use of disulfiram with oral concentrate • Concomitant use of pimozide due to QT prolongation risk
Vortioxetine[90]				
Vortioxetine: oral tablets	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start vortioxetine, do not initiate an MAOI within 21 days of discontinuing vortioxetine) due to serotonin syndrome risk
Vilazodone[88]				
Vilazodone: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age ≥ 12 years: 30 mg daily[b]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk
Serotonin/Norepinephrine reuptake inhibitors (SNRIs)				
Desvenlafaxine[97,214]				
Desvenlafaxine succinate: ER oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age ≥ 7 years: 50 mg daily[b]	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start desvenlafaxine, do not initiate an MAOI within 7 days of discontinuing desvenlafaxine) due to serotonin syndrome risk
Desvenlafaxine: ER oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as desvenlafaxine succinate

[a] *Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.*

[b] *The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)*

[c] *Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*

[d] *The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources*

[e] *The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source*

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Duloxetine[63]				
• Duloxetine delayed release particles: oral capsule • Duloxetine delayed release sprinkle: oral sprinkle	• Fibromyalgia (delayed release particles formulations, including Cymbalta,® only), age 13-17 years. • Generalized anxiety disorder, age 7 or older	• 30-60 mg daily (both oral capsule and sprinkle)	Age ≥7 years: 120 mg daily[b] **or** Age 7-12 years: 60 mg daily[c] Age ≥ 12 years: 120 mg daily[c]	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start duloxetine, do not initiate an MAOI within 5 days of discontinuing duloxetine) due to serotonin syndrome risk
Levomilnacipran[100]				
Levomilnacipran: ER oral capsule	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start levomilnacipran, do not initiate an MAOI within 7 days of discontinuing levomilnacipran) due to serotonin syndrome risk
Milnacipran[102]				
Milnacipran: Oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start milnacipran, do not initiate an MAOI within 5 days of discontinuing milnacipran) due to serotonin syndrome risk
Venlafaxine[68]				
Venlafaxine HCl XR: ER oral capsules, ER oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age 7-12 years: 75-112.5 mg daily (25-39 kg)[c] Age ≥ 12 years: 150 mg daily (40-49 kg), 225 mg daily (>50kg)[c]	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start venlafaxine, do not initiate an MAOI within 7 days of discontinuing venlafaxine) due to serotonin syndrome risk
Venlafaxine HCl: IR Oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age ≥ 6 and < 30 kg: 50 mg daily Age ≥ 6 and ≥ 30 kg: 75 mg daily[68,87,d,e]	• Same as venlafaxine HCl XR
Venlafaxine besylate: ER oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as venlafaxine HCl XR
Dopamine/Norepinephrine-reuptake inhibitor with/without NMDA receptor antagonist				
Bupropion[45,46,111]				
Bupropion HCl IR: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age ≥ 6 years: lesser of 6 mg/kg/day or 300 mg daily[b,c]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Seizure disorder • Current or prior diagnosis of bulimia or anorexia nervosa • Concomitant use of any other bupropion products or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs due to risk of seizure
Bupropion HCl SR: ER (12-hour) oral tablet			Age ≥ 6 years: 400 mg/day [b,c]	
Bupropion HCl XL: ER (24-hour) oral tablet			Age 6-12 years: lesser of 6 mg/kg/day or 300 mg[c] Adolescents: 450 mg [b,c]	

[a] *Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.*

[b] *The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)*

[c] *Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*

[d] *The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources*

[e] *The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source*

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Bupropion hydrobromide: ER (24-hour) oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as bupropion HCl
Bupropion/dextromethorphan: ER oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as bupropion HCl monotherapy
Serotonin reuptake inhibitor/antagonist				
Trazodone[120]				
Trazodone HCl: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age 18 months-3 years: 100 mg daily[83,e] Age 3-5 years: lesser of 3 mg/kg/day or 150 mg daily[83,e] Age ≥ 5 years: 200mg daily[83,e] **or** Adolescents: 100 mg daily[b]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Concomitant use with saquinavir/rotinavir
Nefazodone[119]				
Nefazodone HCl: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Concomitant use with MAOIs (wait at least 14 days after MAOI discontinuation to start nefazodone, do not initiate an MAOI within 7 days of discontinuing nefazodone) due to serotonin syndrome risk. • Coadministration of astemizole, carbamazepine, cisapride, pimozide, terfenadine, or full doses of triazolam • Previous withdrawal of nefazodone due to evidence of liver injury
Serotonin 5-HT1A Receptor Agonist				
Gepirone[113,115]				
Gepirone: ER oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Prolonged QTc interval; > 450 msec at baseline, or congenital long QT syndrome • Concomitant use of strong CYP3A4 inhibitors • Severe hepatic impairment. • Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk
Alpha-2 antagonist				
Mirtazapine[117]				
Mirtazapine: oral tablet, oral disintegrating tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age ≥ 3 years: 45 mg daily [b]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk

[a] Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.

[b] The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)

[c] Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents

[d] The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources

[e] The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Tricyclic, tertiary amine (TCA)				
Amitriptyline[49,50,56]				
Amitriptyline HCl: oral tablet	• Depression, age 12 or older	• 10 mg 3 times a day and 20 mg at bedtime	Age ≥ 5 years: 1.5 mg/kg mg daily[85,e] Age >12 years: 200 mg daily[85,e]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Coadministration with cisapride due to QT interval prolongation and arrythmia risk • Myocardial infarction, during the acute recovery period
Amitriptyline-chlordiazepoxide: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as amitriptyline monotherapy
Amitriptyline-perphenazine: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as amitriptyline monotherapy plus bone marrow depression, concomitant use of other CNS depressants
Clomipramine[91]				
Clomipramine HCl, oral capsule	• Obsessive-compulsive disorder, age 10 or older	• 25 mg daily up to 100 mg daily (max 200 mg daily or 3 mg/kg/day, whichever is less)	Age 10-17 years: 3 mg/kg/day or 200 mg/day, whichever is less[b] **or** Pre-adolescent: 150 mg daily[c] Adolescent: 200 mg daily[c]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk
Doxepin[57]				
Doxepin: oral capsule, oral concentrate	• Anxiety and/or depression associated with alcoholism, age 12 or older. • Anxiety, age 12 or older • Depression, age 12 or older • Psychotic depressive disorders with associated anxiety, including manic-depressive disorders, age 12 or older	• 75-150 mg daily • 75-150 mg daily • 75-150 mg daily • 75-150 mg daily	Age >7: 3 mg/kg/day[74,e] **or** Age > 12: 300 mg daily[57,74,d,e]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Glaucoma, severe urinary retention
Doxepin: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as above

[a] Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.

[b] The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)

[c] Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents

[d] The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources

[e] The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Imipramine[47,48]				
Imipramine HCl: oral tablet	• Nocturnal enuresis, age 6 and older	• Age 6-12 years: 25 mg daily (max 50 mg daily) • Age >12 years: 25 mg daily (max 75 mg daily)	Age 6-17 years: Lesser of 4 mg/kg or 200 mg[c]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Myocardial infarction, during acute recovery period • Hypersensitivity to dibenzazepines • KIDs List: Avoid in children due to risk of sudden cardiac death
Imipramine pamoate: oral capsule	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Same as imipramine HCl
Trimipramine[60]				
Trimipramine: oral capsule	• Depression, adolescents only	• 50 mg daily may increase up to 100 mg daily	Adolescents: 100 mg daily[60,d]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Myocardial infarction, during acute recovery period • Hypersensitivity to dibenzazepines
Tricyclic, secondary amine (TCA)				
Amoxapine[106]				
Amoxapine: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Myocardial infarction, during acute recovery period • Hypersensitivity to dibenzoxazepine compounds
Desipramine[84]				
Desipramine HCl: Oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	Age 7-13 years: Lesser of 3 mg/kg/day or 100 mg daily[72,e] Adolescents: 150 mg daily[72,e]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Myocardial infarction, during acute recovery period • Hypersensitivity to dibenzazepines • KIDs List: Avoid in children due to risk of sudden cardiac death
Nortriptyline[58]				
Nortriptyline: Oral capsules, oral solution	• Depression, adolescents	• 30-50 mg daily	Age ≥ 6 years: Lesser of 2 mg/kg or 100 mg daily[c] **or** Age ≥ 6 years: 3 mg/kg/day or 150 mg daily[75,e]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Acute recovery period after myocardial infarction • Hypersensitivity to dibenzazepines

[a] Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.

[b] The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)

[c] Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents

[d] The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources

[e] The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Protriptyline[59]				
Protriptyline HCl: oral tablet	• Depression, adolescents	• 15 mg daily	Adolescents: 60 mg daily[92,e]	• Coadministration with an MAOI or use within 14 days of MAOI discontinuation due to serotonin syndrome risk. • Acute recovery period after myocardial infarction • Coadministration with cisapride due to QT prolongation risk
Monoamine oxidase inhibitor (MAOI)				
Isocarboxazid[61]				
Isocarboxazid: oral tablet	• Depression, age 16 and older	• Use adult dosing: 20-40 mg daily, max 60 mg daily	Age ≥ 16 years: 60 mg daily[61,d]	• Cardiovascular disorders, hypertension, or patients receiving antihypertensives, or diuretics. • Concurrent administration of antihistaminic, sedative substances, and CNS depressants such as narcotics, barbiturates, and ethanol; dextromethorphan, excessive caffeine, aged foods containing high concentrations of tyramine, sympathomimetic drugs • Concomitant use or use within 14 days of bupropion, sertraline, paroxetine, or other SSRI besides fluoxetine; 10 days of buspirone; 2-3 weeks of meperidine; 5 weeks of fluoxetine; 1 week of other MAOIs or dibenzazepines • History of headache or liver disease, confirmed or suspected cerebrovascular defects, sever impairment of renal function, or pheochromocytoma. • Use with general anesthesia, cocaine, or local anesthesia containing sympathomimetic vasoconstrictors; discontinue within 10 days of elective surgery

[a] Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.

[b] The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)

[c] Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents

[d] The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources

[e] The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Phenelzine[77]				
Phenelzine: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Concomitant use or within 14 days of another MAOI or SSRIs (except fluoxetine), bupropion, or buspirone • Concomitant use of fluoxetine (allow 5 weeks between discontinuing fluoxetine and initiating phenelzine, and 14 days between discontinuing phenelzine and initiating fluoxetine) • Concomitant use of CNS depressants, dextromethorphan, guanethidine, meperidine, or sympathomimetic drugs • Congestive heart failure, liver disease or abnormal liver function tests, pheochromocytoma, renal disease or severe renal impairment • Ingestion of excessive amounts of coffee or chocolate or foods high in tyramine or dopamine • Elective surgery with general anesthesia during or within 10 days
Selegiline[94,109]				
Selegiline HCl: oral capsule, oral tablet, oral disintegrating tablet	• Safety and effectiveness in children aged 12-17 have not yet been established, contraindicated in children under age 12	• Safety and effectiveness in children aged 12-17 have not yet been established, contraindicated in children under age 12	No recommended max dose listed for pediatrics in literature or compendia	• Use is contraindicated in children younger than 12 years, increased risk of hypertensive crisis. • Concomitant use with SSRIs, dual serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants (clomipramine and imipramine), dextromethorphan, meperidine, methadone, pentazocine, propoxyphene, tramadol, carbamazepine, or other MAOIs; wait 4 to 5 half-lives after discontinuation before initiating selegiline; wait at least 2 weeks after selegiline discontinuation before initiating one of the listed agents and wait at least 5 weeks after discontinuation of fluoxetine before initiating selegiline. • Pheochromocytoma
Selegiline: transdermal 24-hour patch	• Safety and effectiveness in children aged 12-17 have not yet been established	• Safety and effectiveness in children aged 12-17 have not yet been established	Age ≥12 years: 12 mg per 24 hours[b]	• Same as oral route

[a] *Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.*

[b] *The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)*

[c] *Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*

[d] *The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources*

[e] *The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source*

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Tranylcypromine[70]				
Tranylcypromine: oral tablet	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Concomitant use of nonselective histamine-1 receptor antagonists, antidepressants, amphetamines and methylphenidate derivatives, sympathomimetic products, triptans, buspirone, carbamazepine, cyclobenzaprine, dextromethorphan, dopamine, hydroxytryptophan, levodopa, meperidine, methyldopa, milnacipran, rasagiline, reserpine, s-adenosyl-L-methionine, tapentadol, tetrabenazine or tryptophan. • After discontinuing a contraindicated antidepressant, allow 4 to 5 half-lives of the drug or any active metabolite to elapse prior to initiating tranylcypromine. After stopping an MAO-inhibitor antidepressant, a time period of at least 1 week or 4 to 5 half-lives of the other MAOI (whichever is longer) should elapse before starting tranylcypromine. After discontinuing tranylcypromine, at least 1 week should elapse before initiating another MAOI (intended to treat major depressive disorder) or other contraindicated antidepressant. • Pheochromocytoma or other catecholamine-releasing paragangliomas
Gamma-Aminobutyric Acid-A (GABA-A) Receptor Positive Modulator				
Brexanolone[62]				
Brexanolone: IV	• Postpartum depression, age 15 or older	• 30 mcg/kg//hr IV infusion, titrated up to 90 mcg/kg/hr, then decreased back down as a continuous IV over 60 hours	> 15 years: 90 mcg/kg/hr[62,d]	• Specific contraindications have not been determined
Zuranolone[121]				
Zuranolone: oral capsule	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Specific contraindications have not been determined
N-Methyl-D-Aspartate (NMDA) Receptor Antagonist				
Esketamine[112]				
Esketamine: nasal spray	• Safety and effectiveness in children have not yet been established	• Safety and effectiveness in children have not yet been established	No recommended max dose listed for pediatrics in literature or compendia	• Aneurysmal vascular disease or history of intracerebral hemorrhage

[a] *Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.*

[b] *The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)*

[c] *Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*

[d] *The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources*

[e] *The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source*

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

Table D1. Antidepressant FDA-Approved Indications, Contraindications, and Dosing in Children and Adolescents

Drug/Dosage Form	FDA Approved Indication(s) per Micromedex[a]	FDA-Approved Usual Dose Range	Max Dosage per Literature [16,35] or Compendia[d,e] (for any indication)	Contraindication(s)
Ketamine[54]				
Ketamine: solution for injection, solution for IV, topical cream	• General anesthesia; Adjunct, age 16 and older • Induction of general anesthesia, prior to the administration of other general anesthetic agents, age 16 and older • Procedural sedation, age 16 and older	• 1-4.5 mg/kg IV or 6.5-13 mg/kg IM • 1-4.5 mg/kg IV or 6.5-13 mg/kg IM • 2 mg/kg IV or 6.5-13 mg/kg IM	No recommended max dose listed for pediatrics in literature or compendia	• Patients for whom a significant elevation in blood pressure would constitute a serious hazard

[a] *Indications are per the drug compendia, Micromedex. Labeled indications per prescribing information may differ slightly.*

[b] *The "Literature Based Maximum Dosage" according to the 2019 Texas Public Behavioral Health Psychotropic Medication Utilization Parameters for Children and Youth (6th Edition)*

[c] *Maximum dosage according to dosing recommendations from the 2022-2023 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents*

[d] *The maximum dose from any indication in Micromedex was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature sources*

[e] *The maximum dose from any indication in Lexicomp was listed if it was either higher than the recommended dose from the literature sources or if no max dose was given in the literature source*

Abbreviations: CNS, central nervous system; DR, delayed release; ER, extended release; FDA, United States Food and Drug Administration; HCl, hydrochloride; hr, hour; IM, intramuscular; IR, immediate release; IV, intravenous; kg, kilogram; MAOI, monoamine oxidase inhibitor; mcg, micrograms; mg, milligrams; SR, sustained release; XL, extended release

APPENDIX E – OFF-LABEL ANTIDEPRESSANT USES IN PEDIATRICS PER THE COMPENDIA MICROMEDEX OR LEXICOMP

Table E1. Off-Label Antidepressant Uses in Pediatrics per Micromedex or Lexicomp

Antidepressant	Possible Off-label Pediatric Uses per Micromedex[a]		Possible Off-label Pediatric Uses per Lexicomp[b]	
	Off-label indication	Studied or suggested dose range	Off-label indication	Studied or suggested dose range
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram[71,78]	• Obsessive-compulsive disorder, 6-17 years (Category B/Class IIb, evidence favors efficacy)	• Age 6-11 years: 10-20mg daily • Age 12-17 years: 10-30 mg daily • Age 13-17 years: 10-40 mg daily, Max 70 mg daily	• Obsessive-compulsive disorder (limited data available)	• Age ≥7 years-17: 10-40 mg daily
			• Anxiety disorders-generalized, social, separation anxiety, or panic disorder (limited data is available)	• Age ≥7 years to 12 years: 10-20 mg daily • Age ≥12 years: 20-40mg daily
	• Panic disorder (Category C, Class IIb, evidence is inconclusive)	• Study dosing: 20 mg daily	• Depression (limited data available; efficacy results variable)	• Age ≥7 years-17: 20-40 mg daily
Escitalopram[55,81]	• No pediatric off-label indications listed		• Social anxiety disorder (limited data available)	• Age ≥7 years: 10-20mg daily
Fluoxetine[51,79]	• Anxiety disorders (overanxious disorder, social phobia, or separation anxiety disorder), 11-17 years (Category B/Class IIb, evidence is inconclusive)	• Age 11-17 years: 10-60 mg daily	• Generalized anxiety, separation anxiety, or panic disorder (limited data is available)	• Age 6 to <12 years: 10-20 mg daily (max 40 mg) • Age ≥ 12 years: 20-40 mg daily (max 60-80 mg)
			• Selective mutism (limited data is available)	• Age ≥ 5 years: 10-20 mg daily (max 60 mg)
	• Bulimia nervosa (Category B/Class IIa, evidence is inconclusive)	• Study dosing, age 12-18 years: 60 mg daily	• Anorexia nervosa (limited data is available)	• Adolescents: 20-60 mg daily
			• Bulimia nervosa (limited data is available)	• Age ≥ 12 years: 20-60 mg daily
Fluvoxamine[64,66]	• No pediatric off-label indications listed		• Major depressive disorder (limited data available)	• Age ≥12 years: 150-300 mg daily
Paroxetine HCl[80,82]	• Obsessive-compulsive disorder, age 7 or older (Category B/Class IIb, evidence favors efficacy)	• IR 10-60 mg daily (mean dose 25.4 mg/day in children and 36.5 mg/day in adolescents)	• Obsessive-compulsive disorder (limited data available)	• IR 10-60 mg daily (overall mean dose was 20.3 mg/day for children and 26.8 mg/day for adolescents)
	• Social phobia, age 8 or older (Category B/Class IIb, evidence favors efficacy)	• IR 10-50 mg daily (mean dose 26.5 mg/day in children and 35 mg/day in adolescents)	• Social anxiety disorder (limited data available)	• IR 10-50 mg daily (mean dose 21.7 mg/day ≤ 12 and 26.1 mg/day ≥ 12)
	• Panic disorder (Category B/Class IIb, evidence is inconclusive)	• No dosing information		
Paroxetine Mesylate[82,95]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Sertraline[53,67]	• Major depressive disorder (Category B/Class IIb, evidence is inconclusive)	• Age 6-17 years: 50-200 mg daily, mean dose 131 mg/day	• Depression (limited data available)	• Age 6-17 years: 50 mg daily is usual effective dose, max 200 mg/day
	• Generalized anxiety disorder (Category A/Class IIb, evidence favors efficacy)	• Age 7-17 years: 25 mg-200 mg daily		
Vortioxetine[89,90]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	

[a] Includes off-label indications with an evidence rating provided by Micromedex, and with a recommendation class of I, IIa or IIb (indications with class III were excluded as they are not recommended).

[b] This use is not officially designated as off-label and given an evidence level rating by Lexicomp; however, Lexicomp lists the indication among pediatric dosing options, with cited evidence being primarily clinical practice guidelines or expert opinion.

[c] Indication is listed in Lexicomp, but is considered not effective and not recommended (recommendation class III) in Micromedex, so the indication is not included in the summary table (Table 1)

Micromedex evidence ratings:

- *Efficacy categories: Effective; Evidence favors efficacy; Evidence is inconclusive // Recommendation classes: I = recommended; IIa = recommended in most cases; IIb = recommended in some cases*
- *Evidence strength categories: A = demonstrated consistent evidence from meta-analysis of RCTs, or multiple, large, good-quality RCTs; B = evidence from meta-analyses with conflicting results, low-quality RCTs, or non-randomized studies; C = expert opinion*

Lexicomp evidence level ratings: Evidence ratings were not given to pediatric indications.

Abbreviations: ER, extended-release; HCl, hydrochloride; IM, intramuscular; IR, immediate-release; IV, intravenous; kg, kilogram; mg, milligram; mcg, microgram; RCT, randomized controlled trial; XR, extended release

Table E1. Off-Label Antidepressant Uses in Pediatrics per Micromedex or Lexicomp

Antidepressant	Possible Off-label Pediatric Uses per Micromedex[a]		Possible Off-label Pediatric Uses per Lexicomp[b]	
	Off-label indication	Studied or suggested dose range	Off-label indication	Studied or suggested dose range
Vilazodone[87,88]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Serotonin/Norepinephrine reuptake inhibitors (SNRIs)				
Desvenlafaxine[96,97,214]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Duloxetine[63,98]	• No pediatric off-label indications listed		• Major depressive disorder (limited data available; efficacy not established)[c]	• Age ≥ 7 to ≤ 17 years: 30-120 mg daily
Levomilnacipran[99,100]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Milnacipran[101,102]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Venlafaxine[68,69]	• Major depressive disorder (Category B, Class IIb, evidence is inconclusive)	• No pediatric dosing information provided	• Major depressive disorder, unipolar (limited data available)	• Age ≥ 12 years: ER (HCl salt) 150mg to max 225 mg daily
	• Attention deficit hyperactivity disorder (Category B, Class IIb, evidence favors efficacy)	• ≤ 30 kg: 50 mg daily • ≥ 30 kg: 75 mg daily	• Attention deficit hyperactivity disorder (limited data available; efficacy results variable)	• Age ≥ 6 years: IR 12.5 -25 mg daily to max 50 mg daily (≤ 30 kg), 75 mg daily (≥ 30 kg) in divided doses
	• Generalized anxiety disorder (Category B, Class IIb, evidence favors efficacy)	• Age ≥ 6 years: ER 37.5 - 75 mg daily, max dose based on weight	• Generalized anxiety disorder, social anxiety, separation anxiety, or panic disorder (limited data available)	• Age ≥ 6 years: ER (HCl salt) 37.5 mg daily to max 112.5 mg (25-<40 kg), 150 mg (40-<50 kg) and 225 mg (≥ 50 kg) daily
	• Social phobia (Category B, Class IIb, evidence favors efficacy)	• Age ≥ 8 years: 37.5 mg to max 225 mg daily, mean dose in study: 2.6 - 3 mg/kg		
Dopamine/Norepinephrine reuptake inhibitor with or without NMDA receptor antagonist				
Bupropion hydrobromide[43,46]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Bupropion HCl[43,45]	• Attention deficit hyperactivity disorder (Category A, Class IIb, evidence favors efficacy)	• Age 6-12 years: IR 3 mg/kg/day to max 6 mg/kg/day	• Attention-deficit/hyperactivity disorder (limited data available	• Age ≥6 years: IR 1.5-3 mg/kg/day, max lesser of 6 mg/kg/day or 300 mg/day. After titrated on IR product, may switch to ER (12 and 24 hour) in corresponding dose
			• Refractory depression (limited data available)	• Age ≥ 8 years: IR 100-300 mg daily, max 400 mg daily • Age ≥ 11 years: ER (12 hour) 2 mg/kg/day up to max 6mg/kg/day, 100-150 mg (max) • Age ≥ 12 years: ER (24 hour) 150-300 mg daily, max 400 mg daily
			• Smoking cessation (limited data available)	• Age ≥ 14 years and weight ≥ 40.5 kg: ER (12 hour) 150- to max 300 mg daily
Bupropion-dextromethorphan[52,111]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	

[a] Includes off-label indications with an evidence rating provided by Micromedex, and with a recommendation class of I, IIa or IIb (indications with class III were excluded as they are not recommended).

[b] This use is not officially designated as off-label and given an evidence level rating by Lexicomp; however, Lexicomp lists the indication among pediatric dosing options, with cited evidence being primarily clinical practice guidelines or expert opinion.

[c] Indication is listed in Lexicomp, but is considered not effective and not recommended (recommendation class III) in Micromedex, so the indication is not included in the summary table (Table 1)

Micromedex evidence ratings:

- *Efficacy categories: Effective; Evidence favors efficacy; Evidence is inconclusive // Recommendation classes: I = recommended; IIa = recommended in most cases; IIb = recommended in some cases*
- *Evidence strength categories: A = demonstrated consistent evidence from meta-analysis of RCTs, or multiple, large, good-quality RCTs; B = evidence from meta-analyses with conflicting results, low-quality RCTs, or non-randomized studies; C = expert opinion*

Lexicomp evidence level ratings: Evidence ratings were not given to pediatric indications.

Abbreviations: ER, extended-release; HCl, hydrochloride; IM, intramuscular; IR, immediate-release; IV, intravenous; kg, kilogram; mg, milligram; mcg, microgram; RCT, randomized controlled trial; XR, extended release

Table E1. Off-Label Antidepressant Uses in Pediatrics per Micromedex or Lexicomp

Antidepressant	Possible Off-label Pediatric Uses per Micromedex[a]		Possible Off-label Pediatric Uses per Lexicomp[b]	
	Off-label indication	Studied or suggested dose range	Off-label indication	Studied or suggested dose range
Serotonin reuptake inhibitor/antagonist				
Trazodone[83,120]	• No pediatric off-label indications listed		• Insomnia, sleep disturbances (limited data available; frequently used in children with comorbid neuropsychiatric disorders)	• Age 18 months-3 years: 1-2 mg/kg/dose at bedtime, max 25 mg/dose • Age 3-5 years: 1-2 mg/kg/dose at bedtime, max 50 mg/dose • Age >5 years: .75-1 mg/kg/dose or 25-50 mg at bedtime, up to max 200 mg/dose
			• Migraine, prophylaxis (limited data available)	• Age ≥ 7 years: 1 mg/kg/day 3 times daily up to 150 mg/dose
Nefazodone[118,119]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Serotonin 5-HT1A Receptor Agonist				
Gepirone[113,114]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Alpha-2 antagonist				
Mirtazapine[116,117]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Tricyclic, tertiary amine (TCA)				
Amitriptyline[56,85]	• Depression, ages 9-12 (Category B/Class IIA, evidence is inconclusive)	• 1 mg/kg/day in 3 divided doses to 1.5 mg/kg/day	• Chronic pain management (limited data available)	• 0.5-2 mg/kg at bedtime
	• Irritable bowel syndrome (Category B, Class IIb, evidence is inconclusive)	• Study dosing: 10-20mg daily	• Cyclic vomiting syndrome, prophylaxis (limited data available)	• Age ≥ 5 years: 1-1.5 mg/kg/day
	• Headache, treatment, and prophylaxis (Category C, Class IIb, evidence is inconclusive)	• 0.1 to 2 mg/kg/day	• Migraine, prophylaxis (limited data available)	• Age ≥ 8 years: 1 mg/kg/day up to 100 mg daily
Amitriptyline-Chlordiazepoxide[50,103]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Amitriptyline-perphenazine[49,104]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Clomipramine[65,91]	• Depression (Category B, class IIB, evidence favors efficacy)	• Study dosing, age 14-18: 200 mg IV pulse dose	• No pediatric off-label indications listed	
Doxepin[57,74]	• No pediatric off-label indications listed		• Depression and/or anxiety, age 7-11 (limited data available; efficacy results variable)	• 1-3 mg/kg/day
Imipramine HCl[48,73]	• Urinary incontinence (Category B, Class IIB, evidence is inconclusive)	• No dosing available	• Attention-deficit/hyperactivity disorder (limited data available; efficacy results variable)	• Age ≥6 years: 1 mg/kg/day to max 4 mg/kg/day or 200 mg daily

[a] Includes off-label indications with an evidence rating provided by Micromedex, and with a recommendation class of I, IIa or IIb (indications with class III were excluded as they are not recommended).

[b] This use is not officially designated as off-label and given an evidence level rating by Lexicomp; however, Lexicomp lists the indication among pediatric dosing options, with cited evidence being primarily clinical practice guidelines or expert opinion.

[c] Indication is listed in Lexicomp, but is considered not effective and not recommended (recommendation class III) in Micromedex, so the indication is not included in the summary table (Table 1)

Micromedex evidence ratings:

- *Efficacy categories: Effective; Evidence favors efficacy; Evidence is inconclusive // Recommendation classes: I = recommended; IIa = recommended in most cases; IIb = recommended in some cases*
- *Evidence strength categories: A = demonstrated consistent evidence from meta-analysis of RCTs, or multiple, large, good-quality RCTs; B = evidence from meta-analyses with conflicting results, low-quality RCTs, or non-randomized studies; C = expert opinion*

Lexicomp evidence level ratings: Evidence ratings were not given to pediatric indications.

Abbreviations: ER, extended-release; HCl, hydrochloride; IM, intramuscular; IR, immediate-release; IV, intravenous; kg, kilogram; mg, milligram; mcg, microgram; RCT, randomized controlled trial; XR, extended release

Table E1. Off-Label Antidepressant Uses in Pediatrics per Micromedex or Lexicomp

Antidepressant	Possible Off-label Pediatric Uses per Micromedex[a]		Possible Off-label Pediatric Uses per Lexicomp[b]	
	Off-label indication	Studied or suggested dose range	Off-label indication	Studied or suggested dose range
			• Depression (limited data available)	• Age ≥ 8 years: 1.5 mg/kg/day to max 5 mg/kg/day • Adolescents: 30 to 40 mg/day up to 100 mg daily max
Imipramine Pamoate[47,73]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Trimipramine[60,93]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Tricyclic, secondary amine (TCA)				
Amoxapine[105,106]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Desipramine[72,84]	• Attention deficit hyperactivity disorder (Category B/Class IIb, evidence favors efficacy)	• 25 mg daily, max 5 mg/kg/day	• Attention deficit hyperactivity disorder (limited data available)	• Age ≥ 7- 13 years: 25 mg daily up to 100 mg/day (max 3 mg/kg/day) • Age ≥ 13 years: 25-100 mg daily, max 150 mg daily
			• Depression	• Age 6-12 years: 1-3 mg/kg/day • Age > 12 years: 25-100 mg daily, max 150 mg daily
Nortriptyline[58,75]	• Depression, children ≥ age 5 (Category B/Class IIB, evidence is inconclusive)	• Age 5-9 years: 20-75mg daily based on plasma level after giving a 25mg dose • Age 10-16 years: 20-100 mg daily based on plasma level after 50 mg dose	• Depression (limited data available for children)	• Age 6-12 years: 1-3 mg/kg/day, max 150 mg daily
	• Attention deficit hyperactivity disorder (Category B/Class IIb, evidence favors efficacy)	• Dosage varied by study (range 10-100 mg daily)	• Attention deficit hyperactivity disorder (limited data available)	• 0.5 mg/kg/day up to 2 mg/kg/day up to 100 mg daily
	• Nocturnal enuresis (Category B/Class IIb, evidence favors efficacy)	• Age 6-7/20-25 kg: 10 mg daily • Age 8-11/25-35 kg: 10-20 mg daily • Age ≥ 11/35-54 kg: 25-25 mg daily	• Enuresis (limited data available)	• Age ≥6 years: 10-20 mg daily up to max dose of 40 mg daily
			• Neuropathic pain (limited data available)	• 0.05-1 mg/kg/dose at bedtime. Max 3 mg/kg/day or 150 mg daily
Protriptyline[59,92]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Monoamine oxidase inhibitor (MAOI)				
Isocarboxazid[61,107]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Phenelzine[77,108]	• Depression, Atypical, non-endogenous, or neurotic (Category B/Class IIa, effective)	• No dosing information listed	• No pediatric off-label indications listed	
Selegiline HCl (oral)[76,109]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Selegiline transdermal[76,94]	• No pediatric off-label indications listed		• Depression, adolescents ≥ 17 years	• Age ≥ 17 follow adult dosing: 6 mg/24-hour patch once daily, may increase to 12 mg/24 hours
Tranylcypromine[70,110]	• Major depressive disorder, second-line therapy (Category B/Class IIb, evidence is inconclusive)	• No dosing information listed	• No pediatric off-label indications listed	

[a] *Includes off-label indications with an evidence rating provided by Micromedex, and with a recommendation class of I, IIa or IIb (indications with class III were excluded as they are not recommended).*

[b] *This use is not officially designated as off-label and given an evidence level rating by Lexicomp; however, Lexicomp lists the indication among pediatric dosing options, with cited evidence being primarily clinical practice guidelines or expert opinion.*

[c] *Indication is listed in Lexicomp, but is considered not effective and not recommended (recommendation class III) in Micromedex, so the indication is not included in the summary table (Table 1)*

Micromedex evidence ratings:

- *Efficacy categories: Effective; Evidence favors efficacy; Evidence is inconclusive // Recommendation classes: I = recommended; IIa = recommended in most cases; IIb = recommended in some cases*
- *Evidence strength categories: A = demonstrated consistent evidence from meta-analysis of RCTs, or multiple, large, good-quality RCTs; B = evidence from meta-analyses with conflicting results, low-quality RCTs, or non-randomized studies; C = expert opinion*

Lexicomp evidence level ratings: Evidence ratings were not given to pediatric indications.

Abbreviations: ER, extended-release; HCl, hydrochloride; IM, intramuscular; IR, immediate-release; IV, intravenous; kg, kilogram; mg, milligram; mcg, microgram; RCT, randomized controlled trial; XR, extended release

Table E1. Off-Label Antidepressant Uses in Pediatrics per Micromedex or Lexicomp

Antidepressant	Possible Off-label Pediatric Uses per Micromedex[a]		Possible Off-label Pediatric Uses per Lexicomp[b]	
	Off-label indication	Studied or suggested dose range	Off-label indication	Studied or suggested dose range
Gamma-Aminobutyric Acid (GABA) A Receptor Positive Modulator				
Brexanolone[41,62]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Zuranolone[42,121]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
N-Methyl-D-Aspartate (NMDA) Receptor Antagonist				
Esketamine[40,112]	• No pediatric off-label indications listed		• No pediatric off-label indications listed	
Ketamine[39,54]	• Pain, acute: Moderate to Severe (Category A, Class IIB, evidence favors efficacy)	• Age 3-13 years, ≤ 50 kg: 1 mg/kg intranasally via nasal atomizer device	• Analgesia, acute pain (limited data available)	• Age ≥3 years: .5-1.5 mg/kg/dose, max 100 mg/dose
	• Procedural sedation, < 16 years	• Age 5 days-10 years: 2 mg/kg IV or 3 mg/kg IM • Age 0-12 years: 2-2.5 mg/kg IM • Age ≤ 15 years: 4 mg/kg IM • Age 1-10 years: 5 mg/kg intranasally	• Sedation/analgesia, procedural, < 16 years old (limited data available)	• Without propofol: Age ≥ 3 months: 4-5 mg/kg IM or 1-2 mg/kg IV or 3-6 mg/kg intranasal or 5 mg/kg oral with midazolam or children 1-8: 1.5-3 mg/kg rectal • With propofol: Age ≥ 3 months: .5-.75 mg/kg of each agent
	• Rapid sequence intubation, Induction (Category C, Class IIb, evidence is inconclusive)	• No dosing given	• Endotracheal intubation (limited data available)	• Pediatrics: IV 1-2 mg/kg

[a] Includes off-label indications with an evidence rating provided by Micromedex, and with a recommendation class of I, IIa or IIb (indications with class III were excluded as they are not recommended).

[b] This use is not officially designated as off-label and given an evidence level rating by Lexicomp; however, Lexicomp lists the indication among pediatric dosing options, with cited evidence being primarily clinical practice guidelines or expert opinion.

[c] Indication is listed in Lexicomp, but is considered not effective and not recommended (recommendation class III) in Micromedex, so the indication is not included in the summary table (Table 1)

Micromedex evidence ratings:

- *Efficacy categories: Effective; Evidence favors efficacy; Evidence is inconclusive // Recommendation classes: I = recommended; IIa = recommended in most cases; IIb = recommended in some cases*
- *Evidence strength categories: A = demonstrated consistent evidence from meta-analysis of RCTs, or multiple, large, good-quality RCTs; B = evidence from meta-analyses with conflicting results, low-quality RCTs, or non-randomized studies; C = expert opinion*

Lexicomp evidence level ratings: Evidence ratings were not given to pediatric indications.

Abbreviations: ER, extended-release; HCl, hydrochloride; IM, intramuscular; IR, immediate-release; IV, intravenous; kg, kilogram; mg, milligram; mcg, microgram; RCT, randomized controlled trial; XR, extended release