Pharmacological Treatment of Early-Onset Schizophrenia: A Critical Review, Evidence-Based Clinical Guidance and Unmet Needs

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ABSTRACT

Early-onset schizophrenia (EOS) – onset before age 18 – is linked with great disease burden and disability. Decision-making for EOS pharmacological treatment may be challenging due to conflicting information from evidence and guidelines and unidentified care needs may remain unmet.

We searched for systematic reviews, meta-analyses and umbrella reviews of EOS pharmacological treatment published in PubMed over the past 10 years and selected five clinical guidelines from Europe, North-America and Australia. Based on predefined outcomes, we critically compared the evidence supporting EOS-approved drugs in Europe and/or in North-America with guidelines recommendations. We also evaluated the coverage of these outcomes to identify unmet needs.

One systematic review, nine meta-analyses and two umbrella reviews (k = 203 trials, N = 81,289 participants, including duplicated samples across selected articles) were retrieved. Evidence supported the efficacy of aripiprazole, clozapine, haloperidol, lurasidone, molindone, olanzapine, quetiapine, risperidone and paliperidone in EOS, all of which obtained approval for EOS either in Europe and/or in North-America. Cognition, functioning and quality of life, suicidal behaviour and mortality and services utilisation and cost-effectiveness were poorly covered/uncovered.

Among the antipsychotics approved for EOS, aripiprazole, lurasidone, molindone, risperidone, paliperidone and quetiapine emerged as efficacious and comparably safe options. Olanzapine is known for a high risk of weight gain and haloperidol for extrapyramidal side-effects. Treatment-resistant patients should be offered clozapine. Future long-term trials looking at cognition, functioning, quality of life, suicidal behaviour, mortality, services utilisation and cost-effectiveness are warranted. Closer multi-agency collaboration may bridge the gap between evidence, guidelines and approved drugs.

* These two authors contributed equally to this work and they should be named conjointly as last authors.
Introduction

Early-Onset Schizophrenia (EOS) – illness onset before 18 years of age – was reported to affect up to 0.5% of adolescents [1] and account for 25% of adolescent psychiatric admissions [2]. Over 0.5% of adolescents living in Western countries have been estimated to take antipsychotics [3].

EOS was linked with poor psychosocial outcomes and disability [4]. Regarding disease burden [5], schizophrenia was found to account for 12.66 million disability-adjusted life years, which has significantly increased over the past three decades [6]. Most importantly, schizophrenia has been associated with increased mortality [7], which has widened over time [8,9], mainly due to inappropriate care [10]. The economic burden of schizophrenia was estimated at 0.02–1.65% of the gross domestic product (GDP), 50–85% of which is attributable to indirect costs [11].

Although early intervention was demonstrated to improve clinical and disease burden-related outcomes [12, 13], there is little guidance about the pharmacological treatment of EOS due to difficulties in translating conflicting randomised-controlled trials (RCTs) results into clinical guidelines recommendations. Drug approval status from public health regulatory authorities, such as the US Food and Drugs Administration (FDA) [14] and the European Medicines Agency (EMA) [15], may also limit the generalisability of RCTs findings. Clinicians may thus be provided with conflicting information from research evidence, guidelines and drug regulatory bodies. This not only challenges decision-making for the treatment, but also relevant care needs may remain unidentified and unmet, resulting in off-label prescription [16].

Two recent umbrella reviews have well-established the efficacy [17] and safety [18] of pharmacological treatments for mental disorders in children and adolescents, including EOS. Hence, we did not intend to provide additional evidence of EOS treatments. Rather, this critical review of EOS pharmacological treatment aimed: i) to provide updated evidence-based clinical guidance and ii) to identify unmet clinical needs.

Methods

Search strategy and selection criteria

We searched for top-tier evidence published in PubMed over the past 10 years using Medical Subjects Headings (MeSH) terms and keywords (“child”, “adolescent”, “schizophrenia”, “psychotic” and “antipsychotic”), including cross-referencing and manual searches of the references. The search was limited by: i) language: English, ii) age: 12–17 years and iii) article type: systematic reviews, meta-analyses and umbrella reviews.

All the abstracts from the initial search were screened by one author (JDLM). The other two authors (SL and CA) independently resolved any conflict by consensus. Inclusion criteria were: i) systematic review, meta-analysis, or umbrella review ii) of any pharmacological treatment for iii) adolescents (age: 12–17 years) iv) with a diagnosis of Schizophrenia Spectrum Disorders*, including schizophrenia, schizoaffective disorder, delusional disorder and psychotic disorder Not Otherwise Specified, according to either International Statistical Classification of Diseases, 10th Revision [19], or Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and Fourth Edition Text Revision (DSM-IV-TR) [20] and Fifth Edition Text Revision (DSM-5) [21] definitions.

Data extraction

The authors validated a predetermined data extraction form by consensus and the first author (JDLM) extracted all the data, namely: first author, year of publication, article type, number of studies, total sample size (N), the average duration of included studies, and primary and secondary outcome(s). Any inconsistency was resolved by the other two co-authors (SL and CA).

Clinical guidelines

Following an expert consensus meeting (SL, CA), we agreed to identify clinical guidelines if: i) they were available in English and ii) made pharmacological treatment recommendations for EOS iii) based on a systematic review, meta-analysis and/or umbrella review.

Outcomes

We predefined twelve outcomes: i) Acceptability, ii) Efficacy, iii) Tolerability, iv) Motor side effects, v) Metabolic side effects, vi) Hyperprolactinemia, vii) Cognition, viii) Functional outcome/Disability, ix) Suicidal behaviour, x) Mortality, xi) Services use and admissions and xii) Cost-effectiveness and economic outcomes.

For each outcome, we linked the evidence supporting specific pharmacological treatments, including drug approval status, with guidelines recommendations, thus synthesising evidence-based guidance on EOS pharmacological treatment (first aim). We also measured the outcomes coverage to identify unmet needs (second aim).

Results

Study selection

The study selection process is detailed in ▶ Fig. 1. Nine meta-analyses [22–30], two umbrella reviews [17, 18] and one systematic review [31] were reviewed (k = 203 trials, N = 81,289 participants from duplicated trials across studies). The characteristics of the studies are summarised in ▶ Table 1.

Approved drugs for early-onset schizophrenia

EMA- [15] and FDA- [14]-approved drugs for EOS, including dose and age range, are detailed in ▶ Table 2, which includes information on two FDA-approved first-generation antipsychotics (FGAs) – haloperidol and molindone – and eight second-generation antipsychotics (SGAs) (FDA- and/or EMA-approved) – aripiprazole, paliperidone, clozapine, risperidone, quetiapine, lurasidone, olanzapine and amisulpride –.

Clinical guidelines

The German S3 Guideline for Schizophrenia [32], the United Kingdom Maudsley Prescribing Guidelines in Psychiatry [33], the US American Academy of Child & Adolescent Psychiatry guideline [34] and the Canadian Schizophrenia Guidelines [35] were selected. We also reviewed the Australian Clinical Guidelines for Early Psychosis [36].
Guidelines characteristics and EOS pharmacological treatment recommendations are presented in Table 3. All reviewed guidelines recommended SGAs - risperidone, olanzapine, lurasidone, aripiprazole, paliperidone and quetiapine- over FGAs due to safety issues [32–36]. No efficacy-based recommendations between FGAs and SGAs were made except for clozapine (EMA-approved, non-FDA-approved), which was only recommended for treatment-resistant patients due to potential side effects [32–36].

Evidence of available pharmacological treatments for each outcome

Table 4 summarises the outcomes coverage, the evidence supporting approved drugs for each outcome and guidelines recommendations.

Five selected articles reported on acceptability [17, 22, 24, 25, 27], all of which supported two antipsychotics - risperidone and paliperidone.

Efficacy was covered by eight selected articles [17, 22, 24–29] which recommended olanzapine, although aripiprazole [17, 22, 24–28] and lurasidone [17, 22, 25] were also supported by those studies. Clozapine was more efficacious than all the other antipsychotics, according to four (out of seven) studies including this drug [17, 22, 25, 26].

Motor side-effects were covered by seven selected studies [18, 22, 23, 25, 27–29]. Aripiprazole [18, 22, 23, 25, 27] and olanzapine [18, 22, 23, 25, 27] were found to be safe. From a metabolic point of view, which was the most covered outcome [18, 22–30], aripiprazole [18, 23–27, 30] and lurasidone [22, 25] showed a safe profile. The least prolactin-increasing drugs, which was addressed by six selected studies [18, 23, 25, 26, 29, 31], were aripiprazole [25, 26, 31], olanzapine [18, 29, 31] and lurasidone [25],ziprasidone and asenapine [17], none of the latter obtained FDA or EMA approval for EOS. Regarding choice of antipsychotic, aripiprazole, lurasidone, molindone, risperidone, paliperidone and quetiapine could be considered safe and effective antipsychotics, all of which are FDA- and/or EMA-approved, while clozapine (EMA-approved, non-FDA-approved) should be offered to treatment-resistant patients. Guidelines recommendations were consistent with research findings, with the exception of lurasidone, which obtained FDA and EMA approval in 2017 and in 2018, respectively, but is yet to be incorporated into guidelines. Therefore, there seems to be a gap between research, drug approval status and guidelines.

Second, a number of unmet care needs and research gaps were identified, namely cognition, functioning, mortality, suicidal behaviour, quality of life, services use and economic outcomes, which warrants further research.

Evidence-based clinical guidance

Informed clinical decision-making has become routine practice and a marker of high quality of care [37]. Although psychological interventions, particularly cognitive-behavioural therapy [38, 39], have been widely recommended for first-episode psychosis (FEP) [40], antipsychotics continue to be the cornerstone of schizophrenia treatment [17]. Guidelines should therefore aid in answering clinical practice questions such as choice of antipsychotic, dose and duration of treatment, that is, “What?”, “How much?” and “For how long?”, respectively.

First of all, the Primum non nocere principle, i.e., safety, becomes paramount in the management of paediatric populations and from a safety perspective, SGAs were recommended over FGAs [32–36], which was well-supported by the evidence [18]. However, one may question whether FGAs-related motor side effects or SGAs-induced metabolic adverse effects should be avoided first [41], which warrants further head-to-head comparisons. For instance, the very first head-to-head trial in children and adolescents with FEP showed...
| First Author | Publication year | Article type | Number of studies | N | Average follow-up (weeks) | Primary outcome(s) | Secondary outcome(s) |
|--------------|------------------|--------------|------------------|---|--------------------------|--------------------|----------------------|
| Pagsberg     | 2017             | NMA          | 12               | 2158 | 7                       | Efficacy:          | Safety – WG:         |
|              |                  |              |                  |     |                          | 1. ARI, PAL, RIS, QUET, OLZ, MOL. | 1. MOL > ARI > ZIPRA |
|              |                  |              |                  |     |                          | 2. ASE, ZIPRA      | 2. PAL > RIS, OLZ    |
|              |                  |              |                  |     | Safety – EPS:            | 1. ASE, OLZ >      |                      |
|              |                  |              |                  |     |                          | 2. ZIPRA, PAL, RIS, PAL, ARI, PAL, RIS, QUET > | 3. MOL.                |
|              |                  |              |                  |     | Acceptability:           | 1. OLZ, PAL, QUE, RIS > all others |                     |
| Druyts       | 2016             | SR           | 11               | 1772 | 6                       | Safety – PRL:      |                       |
|              |                  |              |                  |     |                          | 1. ARI, CLOZ, QUET |                       |
|              |                  |              |                  |     |                          | 2. RIS, OLZ, PAL   |                       |
| Harvey       | 2016             | NMA          | 11               | 1714 | 6                       | Efficacy:          | Safety – WG:         |
|              |                  |              |                  |     |                          | 1. HAL and MOL >   | 1. HAL, MOL, ZIPRA   |
|              |                  |              |                  |     |                          | 2. OLZ, ARI, RIS, PAL, QUET > ZIPRA | 2. RIS, PAL, ARI |
|              |                  |              |                  |     |                          | 3. QUE             | 4. OLZ                |
|              |                  |              |                  |     | Acceptability:           | 1. HAL             |                       |
|              |                  |              |                  |     |                          | 2. QUE             |                       |
|              |                  |              |                  |     |                          | 3. MOL, ZIPRA, RIS, PAL, OLZ, ARI |                       |
| Krause       | 2018             | NMA          | 28               | 3303 | 6                       | Efficacy:          | Safety – WG:         |
|              |                  |              |                  |     |                          | 1. CLZ             | 1. MOL > ZIPRA       |
|              |                  |              |                  |     |                          | 2. RIS, OLZ, ARIP, LUR, ASE | 2. RIS, PAL, ARI |
|              |                  |              |                  |     |                          | 3. HAL, ZIPRA.     | 3. QUE                |
|              |                  |              |                  |     | Acceptability:           | 1. ARI             |                       |
|              |                  |              |                  |     |                          | 2. ASE             |                       |
|              |                  |              |                  |     |                          | 3. LUR             |                       |
|              |                  |              |                  |     |                          | 4. QUE, RIS, HAL and PAL |                       |
|              |                  |              |                  |     | Safety – EPS:            | HAL, MOL, LOX and RIS worse than the others. |                     |
|              |                  |              |                  |     | Social Functioning:      | 1. RIS, ARI, LUR;  |                       |
|              |                  |              |                  |     | QoL: NMA not feasible due to data unavailability. |                       |                      |
| Arango       | 2020             | NMA          | 13               | 2210 | 6                       | Efficacy:          | Safety – WG:         |
|              |                  |              |                  |     |                          | 1. LUR = CLZ, OLZ, QUET, ZIPRA, ARIP, ASE. | 1. LUR >             |
|              |                  |              |                  |     |                          | 2. PAL > ARI > RIS > QUE > OLZ | 2. PAL > ASE > RIS > QUE > OLZ |
|              |                  |              |                  |     | Safety – Motor symptoms: No differences |                       |                      |
|              |                  |              |                  |     | Safety – Dyslipidaemia and Glucose: |                       |                      |
|              |                  |              |                  |     | 1. ZIPRA                 |                       |                      |
|              |                  |              |                  |     | 2. LUR                   |                       |                      |
|              |                  |              |                  |     | 3. OLZ                   |                       |                      |
|              |                  |              |                  |     | AE discontinuation:      | 1. LUR > all others |                       |
|              |                  |              |                  |     | Somnolence/sedation: No differences |                       |                      |
|              |                  |              |                  |     | Acceptability:           | 1. LUR >           |                       |
|              |                  |              |                  |     |                          | 2. ARI, PAL.       |                       |
### Table 1 Continued.

| First Author | Publication year | Article type | Number of studies | N  | Average follow-up (weeks) | Primary outcome(s) | Secondary outcome(s) |
|--------------|------------------|--------------|-------------------|----|--------------------------|--------------------|----------------------|
| Sarkar & Grover | 2013 | MA | 15 | 995 | 6 | Efficacy: | Tolerability: |
| | | | | | | 1. CLZ | FGA-EPSs |
| | | | | | 2. PAL, OLZ, RIS, QUE, ARI, HAL, MOL, FLU. | SGA (Olanzapine and clozapine) – weight gain and glucose |
| Kumar | 2013 | MA | 13 | 1112 | 6–8 | Efficacy: | Safety – WG: |
| | | | | | 1. CLZ | FGA = SGA, with no differences |
| | | | | | 2. PAL, OLZ, RIS, QUE, ARI, HAL, MOL, FLU. | To avoid: OLZ, RIS, CLZ. |
| Cohen | 2012 | MA | 41 | 4015 | 3–12 | Safety – WG: | |
| | | | | | 1. ARI > QUET > RIS > OLZ | Safety – GLU and PRL: |
| | | | | | 2. PER > MOL > HAL > CHEOR. | SGA: RIS, OLZ, QUE; ZIPRA, ARI, AMI, PAL, LUR, CLZ. |
| | | | | | 3. To use ARI | |
| Xia | 2018 | MA | 8 | 457 | 8.5 | Efficacy: RIS = OLZ | Safety – WG: RIS > OLZ |
| | | | | | | Safety – Sedation: RIS > OLZ |
| | | | | | | Safety – Insomnia: RIS > OLZ |
| | | | | | | Safety – PRL: RIS > OLZ |
| | | | | | | Safety – EPS: RIS > OLZ |
| Pringsheim | 2011 | MA | 35 | 2667 | 6–12 | Safety – WG: ARI > QUET > RIS > OLZ | Safety – Dyslipidaemia: CLZ and OLZ worse than the others |
| | | | | | | Safety – GLU: OLZ worse |
| | | | | | | Safety – EPS: RIS worse than all others |
| Solmi | 2020 | UR | 17 | 51108 | NA | Safety – any EPS: RIS > ARI > PAL > OLZ > AMI > MOL > ZIPRA > HAL > Lox | |
| | | | | | | Safety – Asthenia: RIS > HAL |
| | | | | | | Safety – anorexia: ARI |
| | | | | | | Safety – Sedation: ARI > HAL > Lox > CLZ > MOL > PAL > ZIPRA > OLZ |
| | | | | | | Safety – Akathisia: ARI > OLZ > PAL > MOL |
| | | | | | | Safety – Cholesterol: ARI > QUE > OLZ |
| | | | | | | Safety – PRL: QUE > HAL > OLZ > PAL |
| | | | | | | Safety – WG: PAL > ARI > QUE > CLZ > OLZ |
| | | | | | | Safety – GLU: ASE > ARI > RIS |
| Correll | 2021 | UR | 28 | 9778 | 6–8 | Acceptability: | |
| | | | | | 1. PAL, RIS, OLZ | Efficacy: |
| | | | | | 2. LUR, ZIPRA, QUE, ASE, ARI | |
| | | | | | 1. OLZ > RIS > LUR > ARI > QUE > PAL > ASE | Tolerability: LUR > ZIPRA > RIS > ARI > ASE > QUE > OLZ > PAL |

AMI: Amisulpride; ARI: Aripiprazole; ASE: Asenapine; CLZ: Clozapine; EPS: Extrapyramidal symptom; HAL: Haloperidol; Lox: Loxapine; LUR: Lurasidone; MOL: Molindone; MA: Pairwise meta-analysis; NMA: Network Meta-analysis; OLZ: Olanzapine; PAL: Paliperidone; PRL: Prolactin; QUET: Quetiapine; RIS: Risperidone; GLU: Glucose. SR: Systematic review; UR: Umbrella review; ZIPRA: Ziprasidone.
### Table 2: Approved drugs for early-onset schizophrenia: age range and dose.

| Food & Drugs Administration (FDA) | European Medicines Agency (EMA) |
|----------------------------------|----------------------------------|
| **Age range (years)** | **Recommended** | **Dose (mg/d)** | **Age range (years)** | **Recommended** | **Dose (mg/d)** |
|-----------------------------|-----------------|-----------------|-----------------------------|-----------------|-----------------|
| *First-generation*          |                 |                 | *Second-generation*         |                 |                 |
| Haloperidol                 | non-approved    | 0.05 mg/Kg      | Aripiprazole                | ≥ 13            | 2               |
| Molindone                   | non-approved    | 0.075 mg/Kg     | Paliperidone                | < 51 kg → 3     | 6               |
|                            |                 | 10              |                             | ≥ 51 Kg → 3–12  | 3–12            |
|                            |                 | 225             |                             | ≥ 51 Kg → 12    | 0.5             |
|                            |                 |                 |                             | ≥ 51 Kg → 3–12  | 0.5             |
| *Second-generation*         |                 |                 | *Lurasidone*                | ≥ 13            | 20              |
| Paliperidone                | non-approved    | 0.5 mg/Kg       | 80                          | < 51 kg → 3     | 3–6             |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 3               |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 40              |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 40–80           |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 80              |
| *Olanzapine*                | non-approved    | 2.5–5 mg/day     | 10                          | < 51 kg → 3     | 3–6             |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 3               |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 50              |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 10              |
| *Amisulpride*               | non-approved    | 25–50 mg/day     | 20                          | < 51 kg → 3     | 3–6             |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 3               |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
| *Clozapine*                 | non-approved    | 25–50 mg/day     | 20                          | < 51 kg → 3     | 3–6             |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 3               |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
| *Quetiapine*                | non-approved    | 25–50 mg/day     | 20                          | < 51 kg → 3     | 3–6             |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 3               |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
| *Risperidone*               | non-approved    | 25–50 mg/day     | 20                          | < 51 kg → 3     | 3–6             |
|                            |                  |                 |                             | ≥ 51 Kg → 3–12  | 3               |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |
|                            |                  |                 |                             | ≥ 51 Kg → 12    | 80              |

Note: Doses for children and adolescents should be adjusted based on body weight and safety considerations. For patients over 6–12 weeks, long-term trials are lacking and long-term compliance remains unknown. Future trials with sam-
Dysfunction in schizophrenia and can precede psychosis onset [71].

Cognitive deficits have been associated with social proper investment in this area [70].

Low-up periods and low expectations regarding financial returns, which appears to discourage the pharmaceutical industry from which remains unclear. Newly-developed drugs such as cariprazine [68], although non-approved for children and negatively symptoms, which should be tested. Unfortunately, testing adolescents, may have potential benefits for the treatment of negative symptoms, which warrants replication [22].

Only one selected study reported on functioning [25], which showed risperidone to perform better than aripiprazole and lurasidone, and there were no data on quality of life. Long-term trials are needed to capture functioning outcomes or recovery, including school performance/absenteeism, employment and patient satisfaction [26].

Given the significant increase in adolescent suicide rates [74], which accounts for up to 5% of deaths in schizophrenia [75], future trials should include suicidal behaviour-related outcomes and suicidal history should not exclude eligible candidates from RCTs [76]. For instance, clozapine was reported to prevent suicide in adults with schizophrenia [77], which remains to be replicated in EOS. Despite excess mortality of schizophrenia [7] and a potential association of antipsychotic use with fatal cardiac events in adults [78], we found no data on antipsychotics-related mortality in EOS.

Last but not least, in the post-COVID-19-related economic recession [79], future cost-effectiveness studies are particularly needed [26].

### Table 3  Characteristics of included clinical guidelines and pharmacological treatment recommendations for early-onset schizophrenia.

| Continent | Country | Title | Author | Publication date | Abbreviation and reference | Pharmacological treatment Recommendations |
|-----------|---------|-------|--------|------------------|---------------------------|------------------------------------------|
| Europe    | Germany | S3 Guideline for Schizophrenia | German Association for Psychiatry, Psychotherapy and Psychosomatics | 2019 | DCPPN (German Association for Psychiatry, Psychotherapy and Psychosomatics, 2019) | 1. ARI, QUE, PAL, RIS, CLZ (TR)  
2. HAL, OLZ. |
|           | UK      | The Maudsley Prescribing Guidelines in Psychiatry, 13th Edition. | Editors: Taylor, Barnes, Young | 2018 | Maudsley (Taylor et al., 2019) | 1. ARI, QUE, PAL, RIS, OLZ, CLZ (only for TR, OLZ should be tried first)  
2. ASE, ZIPRA (less efficacious than the above drugs)  
3. FGAs should be avoided due to extrapyramidal adverse effects |
| Oceania   | Australia | Australian Clinical Guidelines for Early Psychosis | Orygen, The National Centre of Excellence in Youth Mental Health | 2016 | Orygen (Australian Clinical Guidelines for Early Psychosis, 2016) | 1. ARI, OLZ, RIS, QUE  
2. CLZ (TR) |
| North America | US | Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia | American Academy of Child and Adolescent Psychiatry | 2013 | AACAP (McClellan et al., 2013) | 1. RIS, ARI, QUE, PAL.  
2. OLZ, ZIPRA, HAL.  
3. CLZ (TR) |
|           | Canada  | Canadian Guidelines for Schizophrenia | Abidi, et al. | 2017 | CSG (Abidi et al., 2017) | No clear recommendations, but:  
1. SGAs (rather than FGAs).  
2. OLZ, only as second-line option due to metabolic side effects.  
3. CLZ (only TR cases) |

ARI: Aripiprazole. PAL: Paliperidone. RIS: Risperidone. QUE: Quetiapine. OLZ: Olanzapine. MOL: Molindone. ASE: Asenapine. ZIPRA: Ziprasidone. CLZ: Clozapine. HAL: Haloperidol. ASE: Asenapine. Lox: Loxapine. LUR: Lurasidone. AMI: Amsulpride.
Strengths and Limitations
Although the efficacy [17] and safety [18] of pharmacological treatments for child and adolescent mental disorders have been established, to our knowledge, no previous work has critically examined the gap between evidence, guidelines and drug approval status to date. By taking this critical approach, we managed to provide up-to-date evidence-based guidance on EOS pharmacological treatment and identify relevant unmet care needs.

Table 4  Evidence-based clinical guidance, approval status and guidelines recommendations.

| Outcomes (proportion) | Studies                                                                 | Treatments | EB | EMA | FDA | DGPPN | Maudsley | AACAP | CSG | Oxygen |
|-----------------------|-------------------------------------------------------------------------|------------|----|-----|-----|-------|----------|-------|-----|--------|
| Acceptability (5/12)  | (Arango et al., 2020; Correll et al., 2021; Harvey et al., 2016; Krause et al., 2018; Pagsberg et al., 2017) | AMI 0/5    | NA | NA  | NR  | NR    | NR       | NR    | NR  |
|                       |                                                                         | ARI 3/5    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | CLZ 0/5    | A  | NA  | R   | R     | R        | R     | R   |        |
|                       |                                                                         | HAL 1/5    | NA | A   | R   | NR   | R        | NR    | NR  |        |
|                       |                                                                         | LUR 2/3    | A  | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | MOL 2/5    | NA | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | OLZ 4/5    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | PAL 5/5    | A  | A   | R   | R     | R        | R     | NR  |        |
|                       |                                                                         | QUE 4/5    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | RIS 5/5    | A  | A   | R   | R     | R        | R     | R   |        |
| Efficacy (8/12)       | (Arango et al., 2020; Correll et al., 2021; Harvey et al., 2016; Krause et al., 2018; Kumar et al., 2013; Pagsberg et al., 2017; Sarkar and Grover, 2013; Xia et al., 2018) | AMI 1/7    | NA | NA  | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | ARI 7/7    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | CLZ 4/7    | A  | NA  | R   | R     | R        | R     | R   |        |
|                       |                                                                         | HAL 4/7    | NA | A   | R   | NR   | R        | NR    | NR  |        |
|                       |                                                                         | LUR 3/3    | A  | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | MOL 4/7    | NA | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | OLZ 8/8    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | PAL 5/7    | A  | A   | R   | R     | R        | R     | NR  |        |
|                       |                                                                         | QUE 6/7    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | RIS 7/8    | A  | A   | R   | R     | R        | R     | R   |        |
| Tolerability (2/12)   | (Correll et al., 2021; Sarkar and Grover, 2013)                         | AMI 0/2    | NA | NA  | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | ARI 2/2    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | CLZ 0/2    | A  | NA  | R   | R     | R        | R     | R   |        |
|                       |                                                                         | HAL 0/2    | NA | A   | R   | NR   | R        | NR    | NR  |        |
|                       |                                                                         | LUR 1/1    | A  | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | MOL 0/2    | NA | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | OLZ 0/2    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | PAL 1/2    | A  | A   | R   | R     | R        | R     | NR  |        |
|                       |                                                                         | QUE 1/2    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | RIS 2/2    | A  | A   | R   | R     | R        | R     | R   |        |
| Motor AE (7/12)       | (Arango et al., 2020; Cohen et al., 2012; Krause et al., 2018; Pagsberg et al., 2017; Sarkar and Grover, 2013; Solmi et al., 2020; Xia et al., 2018) | AMI 2/6    | NA | NA  | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | ARI 5/6    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | CLZ 1/6    | A  | NA  | R   | R     | R        | R     | R   |        |
|                       |                                                                         | HAL 0/6    | NA | A   | NR  | NR   | R        | NR    | NR  |        |
|                       |                                                                         | LUR 1/3    | A  | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | MOL 0/6    | NA | A   | NR  | NR   | NR       | NR    | NR  |        |
|                       |                                                                         | OLZ 6/7    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | PAL 3/6    | A  | A   | R   | R     | R        | R     | NR  |        |
|                       |                                                                         | QUE 4/6    | A  | A   | R   | R     | R        | R     | R   |        |
|                       |                                                                         | RIS 3/7    | A  | A   | R   | R     | R        | R     | R   |        |
| Outcomes (proportion) | Studies | Treatments | EB | EMA | FDA | DGPPN | Maudsley | AACAP | CSG | Oxygen |
|-----------------------|---------|------------|----|-----|-----|-------|----------|-------|-----|--------|
| Metabolic AE (10/12)  | (Arango et al., 2020; Cohen et al., 2012; Harvey et al., 2016; Krause et al., 2018; Kumar et al., 2013; Pagsberg et al., 2017; Pringsheim et al., 2011; Sarkar and Grover, 2013; Solmi et al., 2020; Xia et al., 2018) | AMI 1/9 | NA | NA | NR | NR | NR | NR | NR | NR |
|                       |         | ARI 7/9    | A  | A   | R  | R   | R   | R   | R  |
|                       |         | CLZ 2/9    | A  | NA  | R  | NR  | NR  | R   | R  |
|                       |         | HAL 3/9    | NA | A   | R  | NR  | R   | NR  | NR |
|                       |         | LUR 2/3    | A  | A   | NR | NR  | NR  | NR  | NR |
|                       |         | MOL 2/9    | NA | A   | NR | NR  | NR  | NR  | NR |
|                       |         | OLZ 1/10   | A  | A   | NR | R   | NR  | NR  | R  |
|                       |         | PAL 5/9    | A  | A   | R  | R   | NR  | NR  | NR |
|                       |         | QUE 3/9    | A  | A   | R  | R   | R   | R   |
|                       |         | RIS 3/10   | A  | A   | R  | R   | R   |
| Hyperprolactinaemia (6/12) | (Cohen et al., 2012; Druyts et al., 2016; Krause et al., 2018; Kumar et al., 2013; Solmi et al., 2020; Xia et al., 2018) | AMI 0/5 | NA | NA | NR | NR | NR | NR | NR | NR |
|                       |         | ARI 3/5    | A  | A   | R  | R   | R   | R   |
|                       |         | CLZ 1/5    | A  | NA  | R  | R   | R   | R   |
|                       |         | HAL 1/5    | NA | A   | R  | NR  | R   | NR  | NR |
|                       |         | LUR 1/2    | A  | A   | NR | NR  | NR  | NR  | NR |
|                       |         | MOL 0/5    | NA | A   | NR | NR  | NR  | NR  |
|                       |         | OLZ 3/6    | A  | A   | R  | R   | R   | R   |
|                       |         | PAL 0/5    | A  | A   | R  | R   | NR  | NR  | NR |
|                       |         | QUE 2/5    | A  | A   | R  | R   | R   | R   |
|                       |         | RIS 0/6    | A  | A   | R  | R   |
| Cognition (4/12)      | (Arango et al., 2020; Krause et al., 2018; Solmi et al., 2020; Xia et al., 2018) | AMI 0/3 | NA | NA | NR | NR | NR | NR | NR | NR |
|                       |         | ARI 2/3    | A  | A   | R  | R   | R   | R   |
|                       |         | CLZ 3/3    | A  | NA  | R  | R   | R   | R   |
|                       |         | HAL 1/3    | NA | A   | R  | NR  | R   | NR  | NR |
|                       |         | LUR 1/3    | A  | A   | NR | NR  | NR  | NR  | NR |
|                       |         | MOL 1/3    | NA | A   | NR | NR  | NR  | NR  | NR |
|                       |         | OLZ 1/4    | A  | A   | R  | R   | R   | R   |
|                       |         | PAL 1/3    | A  | A   | R  | R   | R   | R   |
|                       |         | QUE 1/3    | A  | A   | R  | R   | R   | R   |
|                       |         | RIS 2/4    | A  | A   | R  | R   | R   | R   |
| Functioning (1/12)    | (Krause et al., 2018) | RIS 1/1    | A  | A   | R  | R   |
|                       |         | ARI 1/1    | A  | A   | R  | R   | R   | R   |
|                       |         | LUR 1/1    | NA | A   | NR | NR  | NR  | NR  | NR |
| Quality of Life (0/12) |         |            |    |     |     |      |      |      |     |
| Suicidal behaviour (0/12) |         |            |    |     |     |      |      |      |     |
| Mortality (0/12)      |         |            |    |     |     |      |      |      |     |
| Services use (0/12)   |         |            |    |     |     |      |      |      |     |
| Cost-Effectiveness (0/12) |         |            |    |     |     |      |      |      |     |

B: Evidence-Based; EMA: European Medicines Agency; FDA: Food and Drugs Administration; DGPPN: German Association for Psychiatry, Psychotherapy and Psychosomatics; AACAP: American Academy of Child and Adolescent Psychiatry; CSG: Canadian Schizophrenia Guidelines; A: Approved; NA: non-approved; R: Recommended; NR: non-recommended; ARI: Aripiprazole; PAL: Paliperidone; RIS: Risperidone; QUE: Quetiapine; OLZ: Olanzapine; MOL: Molindone; ASE: Asenapine; ZIPRA: Ziprasidone; CLZ: Clozapine; HAL: Haloperidol; ASE: Asenapine; LOX: Loxapine; LUR: Lurasidone; AMI: Amisulpride.
This review, however, has several limitations. First, we only searched one major database, namely PubMed. Also, trials excluded from the selected reviews and/or published outside PubMed were not considered. Second, the selection criteria may have been too restrictive. Third, although unnecessary for this review purposes, we did not apply meta-analytic techniques to the findings.

**Final remarks and future directions for research**

This *critical review* of EOS pharmacological treatment permitted us to provide an up-to-date evidence-based guidance. Five SGAs - aripiprazole, lurasidone, quetiapine, risperidone and paliperidone - emerged as safe and effective drugs for EOS. This said, clinical knowledge cannot be substituted by guidelines which can inform, but not dictate, clinical practice. In other words, evidence-based medicine, which provides a certain framework, and personalised medicine should not be considered as two enemies fighting each other [80]. Rather, high-quality care requires a combination of the two. We also highlighted a number of unmet care needs to be addressed by future studies, namely long-term adherence and relapse prevention, negative symptoms, cognition, functioning and quality of life, suicidal behaviour and mortality and service use and economic outcomes. Finally, we identified a gap between evidence, guidelines and drug approval (>Fig. 2). In short, it seems that evidence (e.g., a few small trials) is first needed to establish the safe-
ty and efficacy of a novel drug for it to be approved by drug regulatory bodies, thus encouraging its clinical use and making evidence stronger prior to incorporation into clinical guidelines. However, delays and inconsistencies in this complex process, as revealed by this review, may explain, in part, high off-label prescription rates in EOS. Frequently based on studies on adults [81, 82], off-label prescription raises patient safety and medico-legal issues, hampers future research, limits knowledge of paediatric psychopharmacology and worsens quality of care and clinical outcomes [16].

Regrettfully, drug development in schizophrenia, including EOS, has followed the serendipity path over the past few decades, while illness pathophysiology remains to be integrated into new mechanisms of action. EOS psychopharmacological research may therefore guide the development of new treatments for early- and adult-onset schizophrenia.

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Conflict of Interest

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In the last three years Stefan Leucht has received honoraria as a consultant/advisor and/or for lectures from Angelini, Böhringer Ingelheim, Geodon&Richter, Janssen, Johnson&Johnson, Lundbeck, LTS Lohmann, MSD, Otsuka, Recordati, SanofiAventis, Sandoz, Sunovion, TEVA, Eisai, Rovi, Medichem, Mitsubishi

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