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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 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", "schizophr*", "psycho*" 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

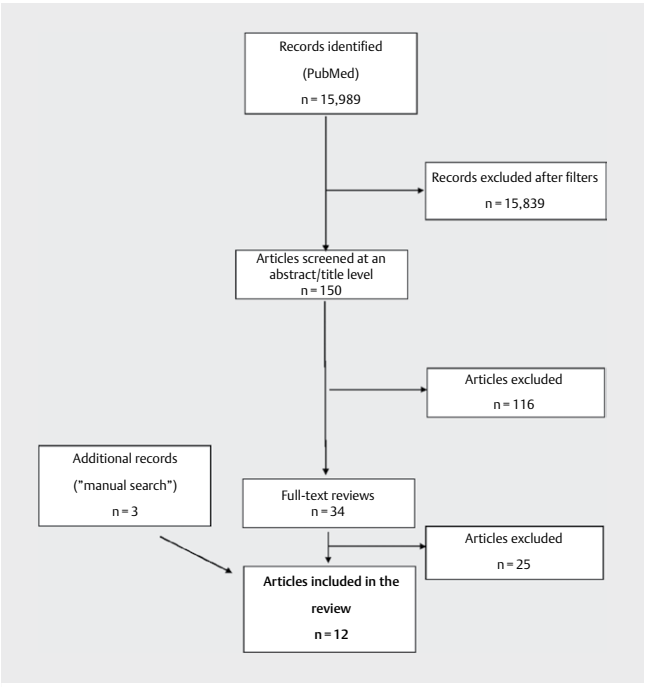
The study selection process is detailed in ▶ **Fig. 1**. Nine meta-analyses [22–30], two umbrella reviews [17, 18] and one systematic review [31] were reviewed (k = 203 trials, N = 81,289 participants from duplicated trials across studies). The characteristics of the studies are summarised in ▶ **Table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



▶ **Fig. 1** Flow-chart of the study selection process.

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, 29] 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].

Outcomes coverage and unmet needs

Metabolic adverse effects (10 studies), *efficacy* (eight studies), *motor adverse effects* (seven studies), *prolactin-related adverse effects* (six studies) and acceptability (five studies) were covered by (at least) almost half of the included studies, while *cognition* (four studies) and *functioning* (one study) were poorly covered. No selected study reported on quality of life, suicidal behaviour, mortality, services use and cost-effectiveness (▶ **Table 4**).

We proposed some suggestions to address the above unmet needs in ▶ **Table 5**, which are discussed further below.

Discussion

Main findings

We carried out a critical review of top-tier evidence, relevant clinical guidelines and drug approval status on EOS pharmacological treatment to provide up-to-date evidence-based clinical guidance and to highlight unmet care needs, from which two main conclusions can be drawn.

First, although psychological interventions were strongly recommended by guidelines, all antipsychotics subject to published RCTs were found to be superior to placebo, with the exception of 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

▶ **Table 1** Characteristics of the selected studies.

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. 2. ASE, ZIPRA	1. MOL > ARI > ZIPRA > 2. PAL > RIS, OLZ
							Safety – EPS:
							1. ASE, OLZ > 2. ZIPRA, PAL, RIS, 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 > 2. OLZ, ARI, RIS, PAL, QUET > ZIPRA	1. HAL, MOL, ZIPRA 2. RIS, PAL, ARI 3. QUE 4. OLZ
							Acceptability:
							1. HAL 2. QUET 3. MOL, ZIPRA, RIS, PAL, OLZ, ARI
Krause	2018	NMA	28	3303	6	*Efficacy:*	*Acceptability:*
						1. CLZ 2. RIS, OLZ, ARIP, LUR, ASE 3. HAL, ZIPRA.	1. PAL, MOL, RIS, OLZ 2. ARI
							Safety – WG:
							1. MOL > ZIPRA > LUR > ARI > ASE > QUET, RIS, PAL 2. CLZ, OLZ, QUE
							Safety - sedation: QUE > LOX, ASE, CLZ.
							Safety – PRL:
							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 > 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 2. PAL, OLZ, RIS, QUE, ARI, HAL, MOL, FLU.	*FGA-EPSs*
							SGA (Olanzapine and clozapine) – weight gain and glucose
Kumar	2013	MA	13	1112	6–8	*Efficacy:*	*Safety – WG:*
						FGA = SGA, with no differences	*To avoid: OLZ, RIS, CLZ.*
						FGA: PER, MOL, HAL, CHLOR.	*Safety – GLU and PRL:*
						SGA: RIS, OLZ, QUE; ZIPRA, ARI, AMI, PAL, LUR, CLZ.	1. To use ARI
Cohen	2012	MA	41	4015	3–12	*Safety – WG: ARI > QUET > RIS > CLZ > OLZ*	
						GLU: OLZ > RIS	
						Dyslipidaemia: OLZ > QUET	
						PRL: ZIPRA > OLZ > RIS	
						EPS: RIS > ARI > OLZ > ZIPRA	
Xia	2018	MA	8	457	8.5	*Efficacy: RIS = OLZ*	*Safety – WG: RIS > OLZ*
							Safety – Sedation: RIS > OLZ
							Safety – Insomnia: OLZ > RIS
							Safety – PRL: OLZ > RIS
							Safety – EPS: OLZ > RIS
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 > RIS > ZIPRA > OLZ	
						Safety – Akathisia: ARI > OLZ > RIS > PAL > MOL	
						Safety – Cholesterol: ARI > QUE > OLZ	
						Safety – PRL: QUE > HAL > OLZ > PAL	
						Safety – WG: PAL > ARI > QUE > CLZ > OLZ	
						Safety – GLU: ASE > RIS > OLZ	
Correll	2021	UR	28	9778	6–8	*Acceptability:*	*Efficacy:*
						1. PAL, RIS, OLZ 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.

	European Medicines Agency (EMA)				Food & Drugs Administration (FDA)			
	Age range (years)	Dose (mg/d)			Age range (years)	Dose (mg/d)		
		Starting	Maximum	Recommended		Starting	Maximum	Recommended
First-generation								
Haloperidol	non-approved				≥ 12	0.05 mg/Kg	0.075 mg/Kg	
Molindone	non-approved				≥ 12	50–75	100	225
Second-generation								
Aripiprazole	≥ 15	2	30	2–10	≥ 13	2	30	10
Paliperidone	≥ 15	3	< 51 kg → 6	< 51 kg → 3–6	≥ 12	3	< 51 kg → 6	< 51 kg → 3–6
			≥ 51 Kg → 12	≥ 51 Kg → 3–12			≥ 51 Kg → 12	≥ 51 Kg → 3–12
Clozapine*	≥ 16	12.5	900	50–200	non-approved			
Risperidone	non-approved (in some European countries, ≥ 15 years)				≥ 13	0.5	6	3
Quetiapine	non-approved				≥ 13	25–50	800	400–800
Lurasidone	≥ 13	20	80	20–80	≥ 13	40	40–80	80
Olanzapine	non-approved				≥ 13	2.5–5		10
Amisulpride	non-approved (could be used in adolescents ≥ 15 years in some European countries)				non-approved			

[a] At the time of submitting the final manuscript of this article, only the above *oral* pharmacological treatments had received FDA or EMA approval for early onset schizophrenia (EOS). *Treatment-resistance: failure to respond to two adequate trials with different antipsychotics at the optimal dose.

olanzapine to cause significantly more weight gain than quetiapine [42]. Indeed, two reviewed guidelines [34, 35] strongly recommended against the first-line use of olanzapine in FEP, including EOS, due to the high risk of metabolic side effects. Also, SGAs were demonstrated to increase the risk of motor side-effects, particularly risperidone-induced tardive dyskinesia [43].

Hence, starting treatment with overall comparably safe antipsychotics, such as aripiprazole [24, 26, 27, 30, 31] or lurasidone [22], thus minimising the risk of adverse effects and enhancing long-term adherence [44], appears to be recommendable [18]. On the other hand, the sometimes still held view among clinicians that FGAs are more efficacious than SGAs was not supported by this review, in line with a Cochrane systematic review [26] and a meta-analysis [45]. Clozapine was replicated as the most efficacious antipsychotic for EOS [17, 22, 25, 26], consistent with a previous systematic review [46]. While only *'treatment-resistant'* cases - those who failed to respond to two trials of different antipsychotics at the optimum dose for at least six weeks [47] - should be offered clozapine owing to the risk of long-term metabolic adverse effects, agranulocytosis and multiple other side-effects [30, 48]; metformin may reduce clozapine-related metabolic risk [49]. Certainly, the '*dopaminergic* (non-clozapine antipsychotics responders) vs. *non-dopaminergic* (treatment-resistant) psychoses' classification [50] may also apply to EOS, which requires further investigation.

In addition, individuals' expectations and safety priorities need to be taken into account. Thus, prolactin-increasing agents, such as risperidone and paliperidone [51], should not be prioritised in the management of sexually active adolescents and/or those with bone mineralisation and physical growth issues.

After choice of antipsychotic (*What?*), clinicians may struggle to determine a safe, although therapeutic, *dose (How much?)*. In adults, doses over 5 mg/day of risperidone equivalent were meta-analytically found to add limited benefit for relapse prevention, while the risk of side effects was significantly higher [52]. Therapeutic drug monitoring through plasma levels, although routine practice in adult psychiatry [53], appears to be of little value in children and adolescents [54]. Future studies addressing methodological issues may improve patient safety [55] by establishing drug concentration-effect relationships [56]. Of note, the dose-plasma levels relationship significantly differs between adults and children and adolescents [57], who should not be considered *"small adults"* in terms of drug elimination from the system.

Finally, (For *how long?*), patients and/or their carers may prompt clinicians to discontinue medication; and such a decision would be supported by some previous research [58]. However, two recent meta-analyses linked antipsychotic doses reduction with an increased risk of relapse and hospitalization [59, 60].

Unmet clinical needs, research gaps and proposed solutions

Several unmet care needs were identified, which need to be addressed by future research, including long-term compliance, cognition, functioning, quality of life, suicidal behaviour and mortality and services use and economic outcomes (▶ **Table 5**).

In addition, the vast majority of included trials followed-up patients over 6–12 weeks. Therefore, *long-term trials are lacking* and long-term compliance remains unknown. Future trials with sam-

▶ **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	DGPPN (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: Amisulpride.

ples of adolescents with EOS may test Long-Acting Injections, which were demonstrated to prevent relapses/admissions and reduce mortality via improved adherence in adults [61, 62]. Truly, *'Drugs do not work if patients do not take them'*[44] and little is known about (lack of) insight, which is linked with compliance in adults [63, 64], in EOS, in which parents' insight may play a part. Most importantly, evidence-based treatments for poor insight in psychosis are lacking [65], including antipsychotics [66], although metacognitive interventions showed more promising results in adults with schizophrenia [67].

Efficacy - symptoms improvement - was mostly assessed with overall measures; hence treatments efficacy for negative symptoms remains unclear. Newly-developed drugs such as cariprazine [68] and pimavanserin [69], although non-approved for children and adolescents, may have potential benefits for the treatment of negative symptoms, which should be tested. Unfortunately, testing newly-developed drugs for negative symptoms requires long follow-up periods and low expectations regarding financial returns, which appears to discourage the pharmaceutical industry from proper investment in this area [70].

Although only four selected studies examined cognition [18, 22, 25, 29], cognitive deficits have been associated with social dysfunction in schizophrenia and can precede psychosis onset [71]. Lurasidone, which lacks affinity for D4 receptors, may improve cognition [72], as shown by a 12-month head-to-head RCT against quetiapine [73], 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].

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	Orygen
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

▶ **Table 4** Continued.

Outcomes (proportion)	Studies	Treatments	EB	EMA	FDA	DGPPN	Maudsley	AACAP	CSG	Orygen
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
		ARI	7/9	A	A	R	R	R	R	R
		CLZ	2/9	A	NA	R	R	NR	NR	R
		HAL	3/9	NA	A	R	NR	R	NR	NR
		LUR	2/3	A	A	NR	NR	NR	NR	NR
		MOL	2/19	NA	A	NR	NR	NR	NR	NR
		OLZ	1/10	A	A	NR	R	NR	NR	R
		PAL	5/9	A	A	R	R	R	R	NR
		QUE	3/9	A	A	R	R	R	R	R
		RIS	3/10	A	A	R	R	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
		ARI	3/5	A	A	R	R	R	R	R
		CLZ	1/5	A	NA	R	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	NR
		OLZ	3/6	A	A	R	R	R	R	R
		PAL	0/5	A	A	R	R	R	R	NR
		QUE	2/5	A	A	R	R	R	R	R
		RIS	0/6	A	A	R	R	R	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
		ARI	2/3	A	A	R	R	R	R	R
		CLZ	3/3	A	NA	R	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	R
		PAL	1/3	A	A	R	R	R	R	NR
		QUE	1/3	A	A	R	R	R	R	R
		RIS	2/4	A	A	R	R	R	R	R
Functioning (1/12)	(Krause et al., 2018)	RIS	1/1	A	A	R	R	R	R	R
		ARI	1/1	A	A	R	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.

▶ **Table 5** Unmet needs, research gaps and proposed recommendations.

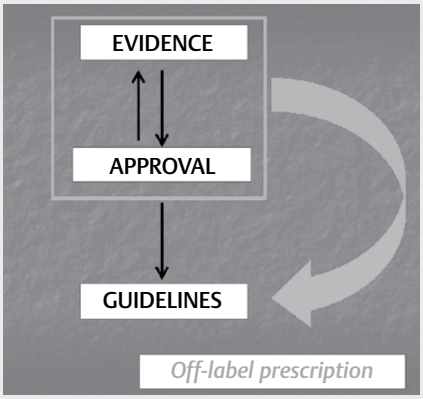
Unmet clinical needs	Research gaps	Proposed recommendations
Long-term efficacy, safety and acceptability/ adherence	Trials follow-up period	To extend trials follow-up period
		Multicenter studies and international collaboration due to anticipated long-term high attrition rates
		Observational studies needed
		Outcomes: relapses, admissions, side effects, functioning, insight (family)
		LAI RCTs and to look at insight as the outcome
		For instance, there are grounds to speculate that aripiprazole LAI, which is available (and approved) in adults, could be safely trialled in adolescents with schizophrenia.
		Theoretical debate about the conceptualization of insight in children and adolescents with EOS, including the role of family members in its development
Efficacy (negative symptoms)	Subscales and individual items do not tend to be looked at as outcome measures	Samples, including patients with predominant negative symptoms.
		Examining subscales or individual items (negative symptoms) as outcome measures.
Cognition	Limited evidence of effects of treatments on cognition	To be looked at in the long-term (comprehensive cognitive tests/tasks)
Functioning	Lack of studies investigating school performance/absenteeism, employment	Future long-term trials should analyse data on functioning-related measures, even in adulthood
Quality of Life (QoL)	Lack of studies looking at QoL as the outcome	QoL scales to be incorporated into routine research protocols of RCTs testing drugs for EOS
Suicidal Behaviour (SB)	High risk excludes suicidal patients from RCTs	Not only suicidal ideation should not be an exclusion criterion from RCTs, but also suicidal ideation, suicide attempts and suicide completions, which are, of course, very tragic and undesirable, should become outcomes of interest in RCTs
	Most RCTs do not examine SB as an outcome.	
Mortality	Lack of mortality data	Long-term trials looking at mortality outcomes
		Observational studies, including nationwide-based cohorts
Services use	Lack of studies on service utilisation and related measures	Admissions, A&E episodes, outpatient appointments,
Cost-effectiveness	Lack of long-term cost-effectiveness studies in the field	
Off-label prescription	Off-label prescription is not a research gap as such. Rather, off-label prescription could be considered as a consequence of all the above research gaps and unmet clinical needs.	To shorten the time from research evidence to approval (bureaucracy).
		Drug regulatory bodies criteria may be too restrictive, although patient safety is paramount, particularly in children and adolescents
Dosing	Limited knowledge and guidance on age-dosing use of EOS treatments in relation to safety and efficacy	Therapeutic drug monitoring studies with age stratification.

LAI: Long-Acting Injections; EOS: Early-onset schizophrenia; QoL: quality of life; RCT: Randomised-Controlled Trial.

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-



▶ **Fig. 2** Identifying gaps between evidence, drug approval and guidelines: off-label prescription.

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].

Regretfully, 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

Javier-David Lopez-Morinigo declares no conflict of interest. Dr. Arango has been a consultant to or has received honoraria or grants from Acadia, Abbot, AMGEN, Angelini, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Forum, Instituto de Salud Carlos III, Gedeon Richter, Janssen Cilag, Lundbeck, Merck, Medscape, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovio and Takeda.
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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