

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



Authors

Javier-David Lopez-Morinigo^{1,2}, Stefan Leucht^{3*}, Celso Arango^{1,2*}

Affiliations

- 1 Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IISGM, CIBERSAM, School of Medicine, Universidad Complutense, Madrid, Spain
- 2 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain
- 3 Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Ismaninger Straße 22, Munich, Germany

Key words

Child, adolescent, schizophrenia, antipsychotics, metanalysis, systematic review

received 15.11.2021

revised 11.04.2022

accepted 29.04.2022

published online 01.07.2022

Bibliography

Pharmacopsychiatry 2022; 55: 233–245

DOI 10.1055/a-1854-0185

ISSN 0176-3679

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Javier-David Lopez-Morinigo
Instituto de Psiquiatría y Salud Mental
Calle Ibiza, 43
Madrid 28009
Spain
jlmorinigo@salud.madrid.org

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 pre-defined 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

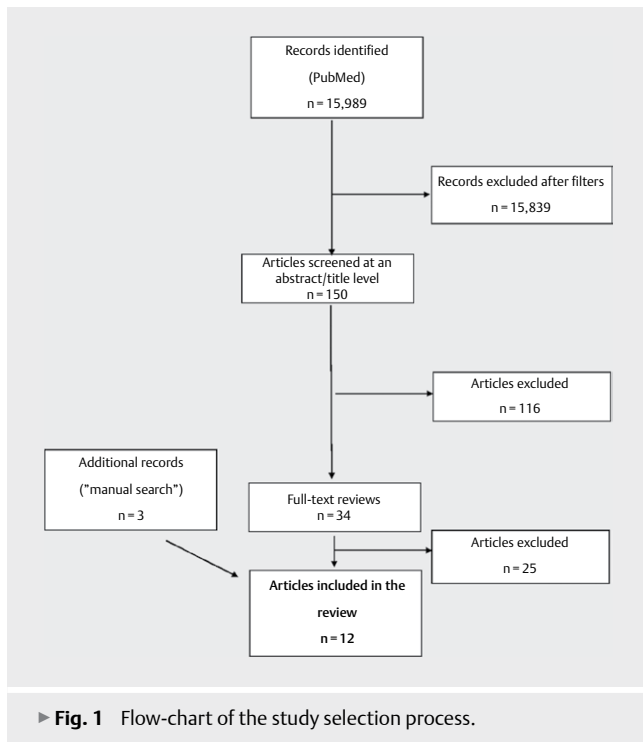
The study selection process is detailed in ► **Fig. 1**. Nine meta-analyses [22–30], two umbrella reviews [17, 18] and one systematic review [31] were reviewed (k = 203 trials, N = 81,289 participants from duplicated trials across studies). The characteristics of the studies are summarised in ► **Table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



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	<i>Efficacy:</i>	<i>Safety – WG:</i>
						1. ARI, PAL, RIS, QUET, OLZ, MOL. 2. ASE, ZIPRA	1. MOL>ARI>ZIPRA> 2. PAL>RIS, OLZ
							<i>Safety – EPS:</i>
							1. ASE, OLZ> 2. ZIPRA, PAL, RIS, ARI, PAL, RIS, QUET> 3. MOL.
						<i>Acceptability:</i>	
							1. OLZ, PAL, QUE, RIS>all others
Druyts	2016	SR	11	1772	6	<i>Safety – PRL:</i>	
						1. ARI, CLOZ, QUET 2. RIS, OLZ, PAL	
Harvey	2016	NMA	11	1714	6	<i>Efficacy:</i>	<i>Safety - WG:</i>
						1. HAL and MOL> 2. OLZ, ARI, RIS, PAL, QUET>ZIPRA	1. HAL, MOL, ZIPRA 2. RIS, PAL, ARI 3. QUE 4. OLZ
							<i>Acceptability:</i>
							1. HAL 2. QUET 3. MOL, ZIPRA, RIS, PAL, OLZ, ARI
Krause	2018	NMA	28	3303	6	<i>Efficacy:</i>	<i>Acceptability:</i>
						1. CLZ 2. RIS, OLZ, ARIP, LUR, ASE 3. HAL, ZIPRA.	1. PAL, MOL, RIS, OLZ 2. ARI
							<i>Safety – WG:</i>
							1. MOL>ZIPRA>LUR>ARI>ASE>QUET, RIS, PAL 2. CLZ, OLZ, QUE
							<i>Safety - sedation: QUE>LOX, ASE, CLZ.</i>
							<i>Safety – PRL:</i>
							1. ARI 2. ASE 3. LUR 4. QUE, RIS, HAL and PAL
							<i>Safety EPS: HAL, MOL, LOX and RIS worse than the others.</i>
							<i>Social Functioning:</i>
							1. RIS, ARI, LUR; QoL: NMA not feasible due to data unavailability.
Arango	2020	NMA	13	2210	6	<i>Efficacy:</i>	<i>Safety - WG:</i>
						1. LUR = CLZ, OLZ, QUET, ZIPRA, ARIP, ASE.	1. LUR> 2. PAL>ASE>RIS>QUE>OLZ
							<i>Safety - Motor symptoms: No differences</i>
							<i>Safety – Dyslipidaemia and Glucose:</i>
							1. ZIPRA 2. LUR 3. OLZ
							<i>AE discontinuation:</i>
							1. LUR>all others
							<i>Somnolence/sedation: No differences</i>
							<i>Acceptability:</i>
	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) Starting	Maximum Recommended	Age range (years)	Dose (mg/d) Starting	Maximum Recommended
<i>First-generation</i>						
Haloperidol	non-approved			≥ 12	0.05 mg/Kg	0.075 mg/Kg
Molindone	non-approved			≥ 12	50–75	100
<i>Second-generation</i>						
Aripiprazole	≥ 15	2	30	≥ 13	2	30
Paliperidone	≥ 15	3	< 51 kg → 6 ≥ 51 kg → 12	≥ 12	3	< 51 kg → 6 ≥ 51 kg → 12
Clozapine*	≥ 16	12.5	900	non-approved		
Risperidone	non-approved (in some European countries, ≥ 15 years)			≥ 13	0.5	6
Quetiapine	non-approved			≥ 13	25–50	800
Lurasidone	≥ 13	20	80	≥ 13	40	40–80
Olanzapine	non-approved			≥ 13	2.5–5	10
Amisulpride	non-approved (could be used in adolescents ≥ 15 years in some European countries)			non-approved		

* 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	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	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	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	R	

► **Table 4** Continued.

Outcomes (proportion)	Studies	Treatments	EB	EMA	FDA	DGPPN	Maudsley	AACAP	CSG	Ory-gen
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 trialed in adolescents with schizophrenia.
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.

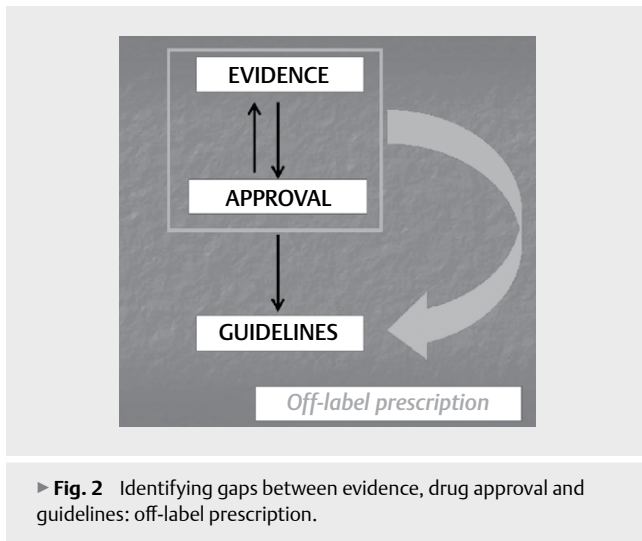
LAI: Long-Acting Injections; EOS: Early-onset schizophrenia; QoL: quality of life; RCT: Randomised-Controlled Trial.

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-



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.

Acknowledgements

We are very grateful to Ethos SL for medical writing support.

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

References

- [1] Masi G, Liboni F. Management of schizophrenia in children and adolescents: Focus on pharmacotherapy. *Drugs* 2011; 71: 179–208. doi:10.2165/11585350-000000000-00000
- [2] James A, Clacey J, Seagroatt V et al. Adolescent inpatient psychiatric admission rates and subsequent one-year mortality in England: 1998–2004. *J Child Psychol Psychiatry* 2010; 51: 1395–1404. doi:10.1111/j.1469-7610.2010.02293.x
- [3] Piovani D, Clavenna A, Bonati M. Prescription prevalence of psychotropic drugs in children and adolescents: An analysis of international data. *Eur J Clin Pharmacol* 2019; 75: 1333–1346. doi:10.1007/s00228-019-02711-3
- [4] Díaz-Caneja CM, Pina-Camacho L, Rodríguez-Quiroga A et al. Predictors of outcome in early-onset psychosis: A systematic review. *NPJ Schizophr* 2015; 1: 14005. doi:10.1038/npschz.2014.5
- [5] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1789–1858. doi:10.1016/S0140-6736(18)32279-7
- [6] He H, Liu Q, Li N et al. Trends in the incidence and DALYs of schizophrenia at the global, regional and national levels: Results from the Global Burden of Disease Study 2017. *Epidemiol Psychiatr Sci* 2020; 29: e91. doi:10.1017/S2045796019000891
- [7] Hjorthøj C, Stürup AE, McGrath JJ et al. Years of potential life lost and life expectancy in schizophrenia: A systematic review and meta-analysis. *Lancet Psychiatry* 2017; 4: 295–301. doi:10.1016/S2215-0366(17)30078-0
- [8] Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. *Annu Rev Clin Psychol* 2014; 10: 425–448. doi:10.1146/annurev-clinpsy-032813-153657
- [9] Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007; 64: 1123–1131. doi:10.1001/archpsyc.64.10.1123
- [10] Lora A, Kohn R, Levav I et al. Service availability and utilization and treatment gap for schizophrenic disorders: A survey in 50 low- and middle-income countries. *Bull World Health Organ* 2012; 90: 47–54. 54A–54B. doi:10.2471/BLT.11.089284
- [11] Chong HY, Teoh SL, Wu DB-C et al. Global economic burden of schizophrenia: A systematic review. *Neuropsychiatr Dis Treat* 2016; 12: 357–373. doi:10.2147/NDT.S96649
- [12] Arango C, Díaz-Caneja CM, McGorry PD et al. Preventive strategies for mental health. *Lancet Psychiatry* 2018; 5: 591–604. doi:10.1016/S2215-0366(18)30057-9
- [13] Correll CU, Galling B, Pawar A et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry* 2018; 75: 555–565. doi:10.1001/jamapsychiatry.2018.0623
- [14] Food and Drugs Administration (FDA). [https://www.fda.gov/drugs] Accessed 5 Nov 2021
- [15] European Medicines Agency (EMA). [https://www.ema.europa.eu] Accessed 5 Nov 2021
- [16] Braüner JV, Johansen LM, Roesbjerg T et al. Off-label prescription of psychopharmacological drugs in child and adolescent psychiatry. *J Clin*

- Psychopharmacol 2016; 36: 500–507. doi:10.1097/JCP.0000000000000559
- [17] Correll CU, Cortese S, Croatto G et al. Efficacy and acceptability of pharmacological, psychosocial, and brain stimulation interventions in children and adolescents with mental disorders: An umbrella review. *World Psychiatry* 2021; 20: 244–275. doi:10.1002/wps.20881
- [18] Solmi M, Fornaro M, Ostinelli EG et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: A large scale systematic meta-review of 78 adverse effects. *World Psychiatry* 2020; 19: 214–232. doi:10.1002/wps.20765
- [19] World Health Organization, WHO. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1993
- [20] American Psychiatric Association American Psychiatric Association, Hrsg. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed., text revision. Washington, DC: American Psychiatric Association; 2000
- [21] American Psychiatric Association American Psychiatric Association, Hrsg. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C: American Psychiatric Association; 2013
- [22] Arango C, Ng-Mak D, Finn E et al. Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: A systematic literature review and network meta-analysis. *Eur Child Adolesc Psychiatry* 2020; 29: 1195–1205. doi:10.1007/s00787-019-01425-2
- [23] Cohen D, Bonnot O, Bodeau N et al. Adverse effects of second-generation antipsychotics in children and adolescents: A Bayesian meta-analysis. *J Clin Psychopharmacol* 2012; 32: 309–316. doi:10.1097/JCP.0b013e3182549259
- [24] Harvey RC, James AC, Shields GE. A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. *CNS Drugs* 2016; 30: 27–39. doi:10.1007/s40263-015-0308-1
- [25] Krause M, Zhu Y, Huhn M et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. *Eur Neuropsychopharmacol* 2018; 28: 659–674. doi:10.1016/j.euroneuro.2018.03.008
- [26] Kumar A, Datta SS, Wright SD et al. Atypical antipsychotics for psychosis in adolescents. *Cochrane Database Syst Rev* 2013; CD009582. doi:10.1002/14651858.CD009582.pub2
- [27] Pagsberg AK, Tarp S, Glintborg D et al. Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2017; 56: 191–202. doi:10.1016/j.jaac.2016.12.013
- [28] Sarkar S, Grover S. Antipsychotics in children and adolescents with schizophrenia: A systematic review and meta-analysis. *Indian J Pharmacol* 2013; 45: 439–446. doi:10.4103/0253-7613.117720
- [29] Xia L, Li W-Z, Liu H-Z et al. Olanzapine versus risperidone in children and adolescents with psychosis: A meta-analysis of randomized controlled trials. *J Child Adolesc Psychopharmacol* 2018; 28: 244–251. doi:10.1089/cap.2017.0120
- [30] Pringsheim T, Lam D, Ching H et al. Metabolic and neurological complications of second-generation antipsychotic use in children: A systematic review and meta-analysis of randomized controlled trials. *Drug Saf* 2011; 34: 651–668. doi:10.2165/11592020-000000000-00000
- [31] Druyts E, Zoratti MJ, Toor K et al. Prolactin-related adverse events and change in prolactin levels in pediatric patients given antipsychotics for schizophrenia and schizophrenia spectrum disorders: A systematic review. *BMC Pediatr* 2016; 16: 181. doi:10.1186/s12887-016-0710-y
- [32] German Association for Psychiatry, Psychotherapy and Psychosomatics. DGPPN e.V. (ed.) for the Guideline Group: S3 Guideline for Schizophrenia. 2019
- [33] Taylor D, Barnes TRE, Young AH. The Maudsley prescribing guidelines in psychiatry. 13th edition Hoboken, NJ: Wiley; 2019
- [34] McClellan J, Stock S. American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolesc Psychiatry* 2013; 52: 976–990. doi:10.1016/j.jaac.2013.02.008
- [35] Abidi S, Mian I, Garcia-Ortega I et al. Canadian guidelines for the pharmacological treatment of schizophrenia spectrum and other psychotic disorders in children and youth. *Can J Psychiatry* 2017; 62: 635–647. doi:10.1177/0706743717720197
- [36] Australian Clinical Guidelines for Early Psychosis. 2016
- [37] Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011
- [38] Devoe DJ, Farris MS, Townes P et al. Interventions and transition in youth at risk of psychosis: A systematic review and meta-analyses. *J Clin Psychiatry* 2020; 81: 17r12053. doi:10.4088/JCP.17r12053
- [39] Mei C, van der Gaag M, Nelson B et al. Preventive interventions for individuals at ultra high risk for psychosis: An updated and extended meta-analysis. *Clin Psychol Rev* 2021; 86: 102005. doi:10.1016/j.cpr.2021.102005
- [40] NICE. Psychosis and schizophrenia in children and young people: Recognition and management. 2013
- [41] Arango C, Giráldez M, Merchán-Naranjo J et al. Second-generation antipsychotic use in children and adolescents: A six-month prospective cohort study in drug-naïve patients. *J Am Acad Child Adolesc Psychiatry* 2014; 53: 1179–1190. doi:10.1016/j.jaac.2014.08.009
- [42] Arango C, Robles O, Parellada M et al. Olanzapine compared to quetiapine in adolescents with a first psychotic episode. *Eur Child Adolesc Psychiatry* 2009; 18: 418–428. doi:10.1007/s00787-009-0749-5
- [43] Garcia-Amador M, Merchán-Naranjo J, Tapia C et al. Neurological adverse effects of antipsychotics in children and adolescents. *J Clin Psychopharmacol* 2015; 35: 686–693. doi:10.1097/JCP.0000000000000419
- [44] Brown FE, David AS. Drugs do not work if patients do not take them. *Eur Neuropsychopharmacol* 2021; 53: 47–48. doi:10.1016/j.euroneuro.2021.07.091
- [45] Zhang J-P, Gallego JA, Robinson DG et al. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: A systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2013; 16: 1205–1218. doi:10.1017/S1461145712001277
- [46] Schneider C, Corrigall R, Hayes D et al. Systematic review of the efficacy and tolerability of clozapine in the treatment of youth with early onset schizophrenia. *Eur Psychiatry* 2014; 29: 1–10. doi:10.1016/j.eurpsy.2013.08.001
- [47] Howes OD, McCutcheon R, Agid O et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry* 2017; 174: 216–229. doi:10.1176/appi.ajp.2016.16050503
- [48] Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *Lancet* 2019; 394: 939–951. doi:10.1016/S0140-6736(19)31135-3

- [49] Ellul P, Delorme R, Cortese S. Metformin for weight gain associated with second-generation antipsychotics in children and adolescents: A systematic review and meta-analysis. *CNS Drugs* 2018; 32: 1103–1112. doi:10.1007/s40263-018-0571-z
- [50] Jauhar S, Veronese M, Nour MM et al. Determinants of treatment response in first-episode psychosis: An 18F-DOPA PET study. *Mol Psychiatry* 2019; 24: 1502–1512. doi:10.1038/s41380-018-0042-4
- [51] Balijepalli C, Druyts E, Zoratti MJ et al. Change in prolactin levels in pediatric patients given antipsychotics for schizophrenia and schizophrenia spectrum disorders: A network meta-analysis. *Schizophr Res Treatment* 2018; 2018: 1543034. doi:10.1155/2018/1543034
- [52] Leucht S, Bauer S, Sifias S et al. Examination of dosing of antipsychotic drugs for relapse prevention in patients with stable schizophrenia: A meta-analysis. *JAMA Psychiatry* 2021. doi:10.1001/jamapsychiatry.2021.2130
- [53] Hiemke C, Bergemann N, Clement HW et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. *Pharmacopsychiatry* 2018; 51: 9–62. doi:10.1055/s-0043-116492
- [54] Whitney Z, Boyda HN, Procyshyn RM et al. Therapeutic drug levels of second generation antipsychotics in youth: A systematic review. *J Child Adolesc Psychopharmacol* 2015; 25: 234–245. doi:10.1089/cap.2014.0044
- [55] Gerlach M, Egberts K, Dang S-Y et al. Therapeutic drug monitoring as a measure of proactive pharmacovigilance in child and adolescent psychiatry. *Expert Opin Drug Saf* 2016; 15: 1477–1482. doi:10.1080/14740338.2016.1225721
- [56] Kloosterboer SM, Vierhout D, Stojanova J et al. Psychotropic drug concentrations and clinical outcomes in children and adolescents: A systematic review. *Expert Opin Drug Saf* 2020; 19: 873–890. doi:10.1080/14740338.2020.1770224
- [57] Fekete S, Hiemke C, Gerlach M. Dose-related concentrations of neuroactive/psychoactive drugs expected in blood of children and adolescents. *Ther Drug Monit* 2020; 42: 315–324. doi:10.1097/FTD.0000000000000685
- [58] Murray RM, Quattrone D, Natesan S et al. Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics? *Br J Psychiatry* 2016; 209: 361–365. doi:10.1192/bjp.bp.116.182683
- [59] Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? *World Psychiatry* 2018; 17: 149–160. doi:10.1002/wps.20516
- [60] Højlund M, Kemp AF, Haddad PM et al. Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia: A systematic review and meta-analysis of randomised controlled trials. *Lancet Psychiatry* 2021; 8: 471–486. doi:10.1016/S2215-0366(21)00078-X
- [61] Kane JM, Correll CU. Optimizing treatment choices to improve adherence and outcomes in schizophrenia. *J Clin Psychiatry* 2019; 80: IN18031AH1C. doi:10.4088/JCP.IN18031AH1C
- [62] Kishimoto T, Hagi K, Kurokawa S et al. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: A systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry* 2021; 8: 387–404. doi:10.1016/S2215-0366(21)00039-0
- [63] David AS. Insight and psychosis. *Br J Psychiatry* 1990; 156: 798–808. doi:10.1192/bjp.156.6.798
- [64] David AS. Insight and psychosis: The next 30 years. *Br J Psychiatry* 2019; 1–3. doi:10.1192/bjp.2019.217
- [65] Pijnenborg GHM, van Donkersgoed RJM, David AS et al. Changes in insight during treatment for psychotic disorders: A meta-analysis. *Schizophr Res* 2013; 144: 109–117. doi:10.1016/j.schres.2012.11.018
- [66] Pijnenborg GHM, Timmerman ME, Derks EM et al. Differential effects of antipsychotic drugs on insight in first episode schizophrenia: Data from the European First-Episode Schizophrenia Trial (EUFEST). *Eur Neuropsychopharmacol* 2015; 25: 808–816. doi:10.1016/j.euroneuro.2015.02.012
- [67] Lopez-Morinigo J-D, Ajnakina O, Martínez AS-E et al. Can metacognitive interventions improve insight in schizophrenia spectrum disorders? A systematic review and meta-analysis. *Psychol Med* 2020; 50: 2289–2301. doi:10.1017/S0033291720003384
- [68] Németh G, Dombi ZB, Laszlovszky I et al. Addressing negative symptoms of schizophrenia pharmacologically with cariprazine: Evidence from clinical trials, a real-world study, and clinical cases. *Expert Opin Pharmacother* 2021; 1–2. doi:10.1080/14656566.2021.1968827
- [69] Bugarski-Kirola D, Arango C, Fava M et al. Pimavanserin for negative symptoms of schizophrenia: Results from the ADVANCE phase 2 randomised, placebo-controlled trial in North America and Europe. *Lancet Psychiatry* 2022; 9: 46–58. doi:10.1016/S2215-0366(21)00386-2
- [70] Gentile S. Clinical usefulness of second-generation antipsychotics in treating children and adolescents diagnosed with bipolar or schizophrenic disorders. *Paediatr Drugs* 2011; 13: 291–302. doi:10.2165/11591250-000000000-00000
- [71] Sommer IE, Bearden CE, van Dellen E et al. Early interventions in risk groups for schizophrenia: What are we waiting for? *NPJ Schizophr* 2016; 2: 16003. doi:10.1038/npschz.2016.3
- [72] Murai T, Nakako T, Ikeda K et al. Lack of dopamine D4 receptor affinity contributes to the procognitive effect of lurasidone. *Behav Brain Res* 2014; 261: 26–30. doi:10.1016/j.bbr.2013.11.036
- [73] Loebel A, Cucchiaro J, Xu J et al. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind, noninferiority study. *Schizophr Res* 2013; 147: 95–102. doi:10.1016/j.schres.2013.03.013
- [74] Miron O, Yu K-H, Wilf-Miron R et al. Suicide rates among adolescents and young adults in the United States, 2000-2017. *JAMA* 2019; 321: 2362. doi:10.1001/jama.2019.5054
- [75] Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: A reexamination. *Arch Gen Psychiatry* 2005; 62: 247–253. doi:10.1001/archpsyc.62.3.247
- [76] Tondo L, Baldessarini RJ. Suicidal behavior in mood disorders: Response to pharmacological treatment. *Curr Psychiatry Rep* 2016; 18: 88. doi:10.1007/s11920-016-0715-0
- [77] Meltzer HY, Alphas L, Green AI et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; 60: 82–91. doi:10.1001/archpsyc.60.1.82
- [78] Papola D, Ostuzzi G, Gastaldon C et al. Antipsychotic use and risk of life-threatening medical events: Umbrella review of observational studies. *Acta Psychiatr Scand* 2019; 140: 227–243. doi:10.1111/acps.13066
- [79] Kawohl W, Nordt C. COVID-19, unemployment, and suicide. *The Lancet Psychiatry* 2020; 7: 389–390. doi:10.1016/S2215-0366(20)30141-3
- [80] de Leon J.. Evidence-based medicine versus personalized medicine: Are they enemies? *J Clin Psychopharmacol* 2012; 32: 153–164. doi:10.1097/JCP.0b013e3182491383
- [81] Persico AM, Arango C, Buitelaar JK et al. Unmet needs in paediatric psychopharmacology: Present scenario and future perspectives. *Eur Neuropsychopharmacol* 2015; 25: 1513–1531. doi:10.1016/j.euroneuro.2015.06.009
- [82] Sharma AN, Arango C, Coghill D et al. BAP Position Statement: Off-label prescribing of psychotropic medication to children and adolescents. *J Psychopharmacol* 2016; 30: 416–421. doi:10.1177/0269881116636107