

Clinical Practice Guideline on the Choice of First Antipsychotic Medicine for Females Experiencing a First-Episode of Psychosis

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Background: Early intervention in first-episode psychosis (FEP) is critical for long-term outcomes with antipsychotic medicines among the primary treatment options. However, existing clinical practice guidelines (CPGs) do not provide sex-specific recommendations, despite females experiencing distinct vulnerabilities to antipsychotic side-effects. In particular, hyperprolactinemia and cardiometabolic side-effects are associated with substantial subjective distress and potential long-term physical health risks for females across the reproductive lifespan. We aimed therefore to develop a CPG on the preferred antipsychotic medicines for females experiencing FEP.

Study Design: An international multidisciplinary panel, including experts-by-experience, used the

GRADE-ADOLOPMENT process and AGREE II framework to adapt existing FEP guidelines for adults and adolescents. Key health questions were developed through stakeholder consultation and literature review. Critically important patient outcomes were prioritized, and evidence was synthesized on side-effect profiles, with recommendations agreed by consensus. The guideline algorithm was field-tested and externally reviewed by experts.

Study Results: Prolactin-elevation and cardiometabolic side-effects were prioritized in antipsychotic medicine selection for females. Medicines with higher risks—first-generation antipsychotics, olanzapine, quetiapine, risperidone, paliperidone, and amisulpride—are not recommended first-line. Aripiprazole is recommended

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as the preferred first-choice due to its consistently favorable prolactin and cardiometabolic profile. Alternative options with low or low-to-medium risk profiles are recommended for adults and adolescents, supported by shared decision-making tools.

Conclusions: This is the first CPG addressing antipsychotic choice for females with FEP. By prioritizing critically important patient outcomes and lived experience, the guideline supports safer, sex-sensitive prescribing for females that may improve treatment acceptability, adherence, and equity in psychosis care.

Key words: first-episode psychosis; female; patient-centered care; antipsychotic medicine; shared decision-making.

Note on terminology:

Following a discussion among the guideline development group and our expert-by-experience collaborators, we agreed to use the term “female” in this guideline to refer to both women and girls whose biological sex at birth was female.

Introduction

The median age of onset of psychosis is 20 years, however, symptom onset is often later in females, with a second peak after age 50.^{1–6} Psychotic disorders are recognized among the most severe and debilitating health conditions.^{7,8} Early intervention at first onset of symptoms is considered the gold standard of care as reducing the duration of untreated psychosis can improve clinical, functional, and social outcomes.^{6,9–12} Early intervention services offer psychological, social, occupational, and educational interventions, alongside antipsychotic medicines as a primary treatment for first-episode psychosis.^{13–15}

Clinical practice guidelines (CPGs) support the translation of research evidence into clinical practice. Several CPGs exist for the management of first-episode psychosis. Except for clozapine (not first-line), evidence suggests minimal differences in efficacy between second-generation antipsychotic medicines in first-episode psychosis. Therefore, current guidelines recommend selection of first medicine as a shared decision incorporating clinician opinion, medicine availability, and individual preferences regarding benefits and side-effects.^{13,16} Approximately half of those presenting with first-episode psychosis are treated in community settings where there is an opportunity to offer the medicines with the most favorable side-effect profiles.¹⁷ Some CPGs favor second-generation antipsychotic as first-choice due to their more acceptable side-effects, particularly considering neurological side-effects.^{16,18–20} Others recommend avoiding olanzapine first-line (especially for younger individuals) due to the significant risk of metabolic side-effects and weight gain.^{16,18–24} A specific guideline for females is needed

to enhance current CPG recommendations and ensure that outcomes that are critically important to females are considered in the recommendation process.

Given the large number of available antipsychotic medicines, it is not considered feasible to comprehensively discuss the benefits and side-effects of all options within a single clinical encounter, especially with those who have no prior exposure to antipsychotic medicines.²⁵ International prescribing data consistently show that antipsychotic use in first-episode psychosis is concentrated among a small number of medicines, namely olanzapine, risperidone, paliperidone, amisulpride, quetiapine and aripiprazole.^{26–31} In some countries, olanzapine remains the most frequently prescribed first-line agent.^{26,27,30,32} However, evidence indicates that removing olanzapine as a first-line option within CPGs is associated with reduced prescribing.³³ Similarly, medicine-specific recommendations delivered through shared decision-making are associated with improved prescribing quality and better clinical outcomes compared with non-directive guidance to prescribe any second-generation agent.³⁴ Rather than restricting choice, these approaches aim to organize medicines into categories and highlight preferred options to support informed shared decision-making. Overall, while CPGs broadly support the use of any second-generation antipsychotic, prescribing practice remains narrowly focused, and greater specificity within guidelines appears to improve care.

Current CPGs remain limited in their ability to account for biological variability, particularly sex differences, including how females experience side effects and what they consider most important in the decision-making process. Due to the historical under-representation of females in preclinical and clinical trials, existing CPGs are primarily based on studies conducted in predominantly male populations and do not provide sex-specific recommendations.^{35–37} Consistent with this, sex-differences in antipsychotic efficacy remain insufficiently studied to guide medicine choice. A recent systematic review reported only limited evidence of superior efficacy of olanzapine in females, with no consistent sex-based efficacy differences identified for any other antipsychotic medicines.³⁸ Current CPGs also fail to consider the overlap between peak age of onset of psychosis and peak fertility in females. Additionally, sex differences in pharmacokinetics and pharmacodynamics may influence antipsychotic tolerability and safety.^{39,40} As early treatment experiences strongly influence adherence and outcomes, antipsychotic medicines optimization for females experiencing first-episode psychosis is vital.⁴¹

Hyperprolactinemia occurs with many antipsychotic medicines with both symptomatic and asymptomatic consequences.⁴² Although evidence for sex-differences in prevalence is mixed, females consistently experience greater magnitudes of prolactin elevation than males.^{43–48} Adolescents appear particularly vulnerable to this side-effect.⁴⁹ For females, symptomatic consequences include amenorrhea, galactorrhea, sexual dysfunction, and infertility, which

are reported among the most subjectively distressing antipsychotic side-effects and are associated with loss of the feeling of femininity and reduced quality of life.^{50–52} The asymptomatic consequences of antipsychotic-induced hyperprolactinemia are understudied. Large cohort studies have reported decreased bone mineral density (impaired attainment of peak bone mass in <25 years), increased risk of osteopenia, osteoporosis, and fractures in females exposed to prolactin-raising agents as well as severely increased breast cancer odds (20% after 1–4 years and 47%–56% after ≥5 year).^{49,53–55} Additionally, as high prolactin levels suppress estrogen production, hyperprolactinemia may also worsen psychotic symptoms and cognition in females.⁵⁶

While cardiometabolic side-effects do not appear more common in females overall, sex differences in antipsychotic-induced weight gain remain inadequately explored.⁵⁷ Qualitative studies show weight gain is highly distressing for females, undermining body image, self-esteem and adherence and a preference for more proactive strategies to prevent antipsychotic-induced weight gain has been expressed.^{58–60} Concerns about long-term cardiometabolic health as a result of weight gain have also been reported which are valid given the significant contribution of weight gain to cardiometabolic risk and all-cause mortality.^{59,61–63}

In light of these sex-specific risks and subjective side-effect burdens, we developed a CPG to inform first-choice antipsychotic medicine for females experiencing first-episode psychosis.

Methods

This guideline is an adaptation of existing recommendations to consider patient important outcomes for females when assessing the balance of risk and benefit in choice of antipsychotic treatment for first-episode psychosis. The GRADE-ADOLOPMENT process was followed.⁶⁴ The manuscript has been written using the RIGHT-Ad@pt checklist for reporting adapted healthcare guideline recommendations and with reference to the AGREE II and AGREE-REX standards for CPGs.^{65–67} A summary of the guideline development process mapped to the AGREE II criteria is outlined in Table S1.1.

Scope and Purpose

The purpose of this CPG is to provide evidence-based recommendations for the choice of antipsychotic medicine for females experiencing a first-episode of psychosis. Key health questions were devised (Table 1). We aim to provide accessible information to clinicians, service users, and caregivers to support shared decision-making and implementation of the recommendations. The recommendations are for young females aged 13–17 years and adults 18 years and older. Recommendations apply to inpatient and community settings. An individual perspective is taken and therefore the judgments are based on the balance of expected benefits and harms, the certainty of the evidence, and acceptability, preferences, and values of those to whom the recommendations apply. Population level considerations such as equity,

feasibility, and resource utilization were considered, particularly in relation to availability of newer medicines.

The Guideline Development Group

The guideline development group (GDG) consisted of international researchers and clinicians with expertise in women's health, adult psychiatry, child and adolescent psychiatry and early intervention psychosis programs. All guideline group members practice in high income countries. We used the EVOLVE framework to ensure the meaningful involvement of our experts-by-experience at the optimum stages of guideline production and to routinely embed their preferences and values within the CPG.⁶⁸ Our experts-by-experience panel were involved in identifying the topic for guideline consideration, identifying important outcomes, generating recommendations, iteratively reviewing and developing the resulting algorithm and co-designing information videos to support guideline implementation. Conflicts of interest disclosures were gathered and reviewed by the guideline chair (BOD)—[Supplementary Material 2](#). No action was required to manage conflicts of interest.

Source Guideline Identification

A previously published systematic review of guidelines for the pharmacological treatment of first-episode psychosis in adults was partially updated with a search of guideline repositories in February 2025 (Table S1.3A).¹⁶ A separate systematic search was conducted to identify source guidelines for the pharmacological treatment of psychosis in young people <18 years (Table S1.3B). All guidelines were reviewed for currency, quality, and development approach. Guidelines were assessed for quality using the AGREE II criteria by 2 independent reviewers and a third reviewer resolved any disagreement (DK, CHR, and AC).⁶⁶ Only guidelines that scored 60% or more on “Domain 3: Rigor of Development” were considered as source guidelines. Guidelines with a full evidence synthesis, compatible with GRADE and structured Evidence to Decision approach were preferred as they are most useful in the GRADE-ADOLOPMENT process.^{64,69} Data extracted from current guidelines included the method of development and the findings for the key health question of antipsychotic choice for females experiencing first-episode psychosis.

Development of Guideline Recommendations

Patient important outcomes from existing guidelines were reviewed by the GDG. A working group (CHR, DK, AC, BOD, FMCN, YH) reviewed the recommendations from existing guidelines, adapted the Evidence to Decision Framework ([Supplementary Material 3](#)) and summarized the information in an algorithm for presentation to the GDG. Decisions were made by consensus. All panel members agreed on the final recommendations, the strength of the recommendations (Table 2) and algorithm. The guideline was field tested by members of the GDG at several stages throughout

Table 1. Key Health Questions

1.1	Which patient-important outcomes should be considered for females experiencing first-episode psychosis?
1.2	Which antipsychotic medicines are associated with a higher risk of prolactin-elevating and cardiometabolic side-effects and should be avoided first-line in females?
1.3	Which antipsychotic medicines are associated with a lower risk of prolactin-elevating and cardiometabolic side-effects and are preferred first-line in females?

Table 2. GRADE—Grades of Recommendation, Assessment, Development, and Evaluation⁷⁰

Target audience	Strong recommendation	Conditional recommendation
For patients/public	We believe most people in this situation would want the recommended course of action and only a small number would not	We believe that most people in this situation would want the recommended course of action, but many would not. Different choices are acceptable for each person, and clinicians should support patients and discuss their values and preferences to reach a decision. Decision aids may support people in reaching these decisions.
For clinicians	The recommendation would apply to most individuals. Formal discussion aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	We recognize that different choices may be appropriate for individual patients. Clinicians should support each patient in reaching a management decision consistent with his or her values and preferences. Decision aids may support individuals in reaching such decisions.
For policy makers and developers of quality measures	The recommendation can be adapted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator	Policymaking will require substantial debate and involvement of various stakeholders. An appropriately documented decision-making process could be used as a quality indicator.

the process to elicit feedback and gauge acceptability. This field testing was carried out among consultant psychiatrists working in both inpatient and outpatient settings, advanced specialist mental health pharmacists working in an inpatient setting and the experts-by-experience panel. A final external review was conducted by two psychiatrists.

Results

Female-Specific Recommendations in Existing CPGs

On reviewing existing CPGs, we determined that there were no female-specific recommendations regarding choice of first antipsychotic medicine (Tables 1.3A and 1.3B).

Guideline Recommendations

Patient Important Outcomes. Up to 80% of those with first-episode psychosis respond to their first antipsychotic medicine.⁷¹ Evidence indicates that there is no one agent with significant superiority in terms of efficacy in this population.⁷² CPGs therefore recommend that the choice of first antipsychotic be based on the individual preferences regarding side-effects.^{13,14,16,73–75}

The GDG agreed that the critically important patient outcomes of hyperprolactinemia and cardiometabolic side-effects, particularly weight gain, should be prioritized in the Evidence to Decision Framework. Existing CPGs already address neurological side-effects by preferentially

recommending second-generation over first-generation antipsychotic medicines, reflecting evidence that strong D2 receptor blockade is associated with extrapyramidal symptoms. While these outcomes have been extensively considered, hyperprolactinemia has been less consistently prioritized. The GDG therefore designated hyperprolactinemia and cardiometabolic side-effects, particularly weight gain, as critically important outcomes in the Evidence to Decision Framework. Other side-effects, including anticholinergic and sedative effects, were considered but assigned lower priority based on relative subjective burden and potential for physical harm. The evidence of harm associated with antipsychotic-induced hyperprolactinemia—specifically the increased risk of fractures and the increased risk of breast cancer—is of low certainty (Supplementary Material 3). However, the GDG considered the link with patient important outcomes, including amenorrhea, galactorrhea, sexual dysfunction, infertility, increased risk of fractures due to osteoporosis, and increased risk of breast cancer, to be sufficiently established to use raised prolactin levels as a surrogate measure. According to the GRADE handbook, when important outcomes are relatively infrequent or emerge over long periods of time, surrogate markers are acceptable but may lead to a rating down of the certainty of the evidence.⁷⁰

A judgment was made in consultation with our experts-by-experience that most females would choose to avoid medicines with a high certainty of raised prolactin or cardiometabolic side-effects.

Table 3. Prolactin-Elevating and Cardiometabolic Risk of Antipsychotic Medicines to Avoid and Preferred Medicines (See Standard Mean Differences in Supplement 3)

Medicine	Hyperprolactinemia risk	Cardiometabolic risk	Preferred choice for females with first-episode psychosis?
Amisulpride	High	Low	No
First-generation antipsychotic medicines	High	Low	No
Olanzapine	High (Under 18 s)	High	No
Paliperidone	High	Medium	No
Quetiapine	Low	High	No
Risperidone	High	Medium	No
Aripiprazole	Lowest	Lowest	Yes—first-choice
Brexpiprazole	Low	Low	Yes
Cariprazine	Low	Low	Yes—for adults
Lurasidone	Low-medium	Low	Yes
Asenapine	Low	Low-medium	Yes—for adults
Ziprasidone	Low-medium	Low	Yes—for adults

Recommendation 1: For females experiencing a first-episode of psychosis we do not recommend the following medicines as first-choice antipsychotic due to a relatively higher risk of extrapyramidal, cardiometabolic and hormonal side effects: first-generation antipsychotics, clozapine, olanzapine, quetiapine, risperidone, paliperidone and amisulpride.

(Strong recommendation against)

High Risk Cardiometabolic Side-Effects in Adults. Clozapine and olanzapine are consistently associated with the highest risk of weight gain in adults with quetiapine, risperidone, and paliperidone having a lower but still significant potential to cause clinically significant increases in weight.^{76,77} Clozapine and olanzapine are also associated with the highest risk of glucose dysregulation in adults.⁷⁶ While both, along with quetiapine also carry the highest risk of dyslipidaemia.⁷⁶

High Risk Cardiometabolic Side-Effects in Adolescents. For adolescents, weight gain was more common with olanzapine, quetiapine, clozapine, risperidone, and paliperidone than with other antipsychotic medicines.^{78–82} Glucose and lipid alterations were greater for children and adolescents with quetiapine and olanzapine than with other antipsychotic medicines.^{76,78}

High Risk Prolactin-Elevating Side-Effects in Adults. Multiple network meta-analyses have evaluated the risk of antipsychotic-induced hyperprolactinemia in adults with amisulpride, risperidone, paliperidone, and first-generation antipsychotics consistently demonstrating the highest risk.^{49,78,83}

High Risk Prolactin-Elevating Side-Effects in Adolescents. Among adolescents, risperidone and paliperidone ranked

highest in terms of associated prolactin elevation.^{78,84} Olanzapine also carries a high risk of prolactin elevation in those under aged 18 years.^{49,78} Of note, there have been no trials of amisulpride or sulpiride in adolescents.

Recommendation 2: For females experiencing a first-episode of psychosis, we recommend aripiprazole as the preferred medicine. For adult females, brexpiprazole and cariprazine* are also recommended with brexpiprazole an option for females aged 13–17 years. Lurasidone, asenapine and ziprasidone are the preferred dopamine antagonists with lurasidone an option for females aged 13–17 years. (Choice may be guided by availability/accessibility/affordability).

*Highly effective (user independent) contraceptive methods are recommended during treatment with cariprazine and for at least ten weeks following the last dose of cariprazine.

Aripiprazole. Aripiprazole is a partial D2 agonist and 5-HT2A antagonist that poses the lowest risk for cardiometabolic difficulties and raised prolactin in both adolescents and adult populations.^{42,76,78,83,85} It is considered the safest treatment option for females experiencing first-episode psychosis. The safety and effectiveness of aripiprazole has been established in both adults and adolescents (Table 4). Aripiprazole has a long half-life of >75 h and may take longer to reach steady state (approximately 2 weeks) resulting in a longer time-to-effect. This longer half-life, along with the partial D2 agonist properties, are an important advantage to aripiprazole. They contribute to the significantly lower relapse rates as compared to other antipsychotic medicines when aripiprazole is gradually discontinued by guided gradual tapering.⁸⁶ Another benefit of aripiprazole is its availability in both oral (daily) and long-acting injectable formulations (monthly or 2-monthly).^{87,88} Long-acting injections are associated with a 32% lower risk of relapse and re-hospitalization.⁸⁹

Table 4. Details of Licensing and Indications for Antipsychotic Medicines in Ireland/EU, UK, US, Canada, and Australia

Medicine	IRE/EU (1)	UK (2)	US (3)	Canada (4)	Australia (5)
Aripiprazole	13+ Mania (Up to 12 weeks) 15+ Schizophrenia 18+ Bipolar mania	13+ Mania (Up to 12 weeks) 15+ Schizophrenia 18+ Bipolar mania	6+ Irritability in Autism 6+ Tourette's 10+ Mania	13+ Mania (Up to 12 weeks) 15+ Schizophrenia 18+ Adjunctive Treatment of Major Depressive Disorder 13+ Schizophrenia 18+ Adjunctive Treatment of Major Depressive Disorder 18+ Adjunctive treatment of major depressive disorder 18+ Agitation associated with dementia due to Alzheimer's disease	18+ Schizophrenia 18+ Bipolar I disorder
Brexpiprazole	13+ Schizophrenia	NO	13+ Schizophrenia 18+ Adjunctive treatment of major depressive disorder 18+ Agitation associated with dementia due to Alzheimer's disease		18+ Adjunctive treatment of major depressive disorder 18+ Agitation associated with dementia due to Alzheimer's disease
Cariprazine	18+ Schizophrenia	18+ Schizophrenia	13+ Schizophrenia (as of December 18, 2025) 10+ Manic or mixed episodes associated with bipolar I disorder (as of December 18, 2025) 18+ Bipolar depression 18+ Adjunctive therapy to antidepressants for the treatment of major depressive disorder 10+ MDD	18+ Schizophrenia 18+ Manic or mixed episodes associated with bipolar I disorder 18+ Bipolar depression	18+ Schizophrenia
Lurasidone	13+ Schizophrenia	13+ Schizophrenia		13+ Depressive episodes associated with bipolar I disorder 15+ Schizophrenia 18+ Schizophrenia 18+ Manic or mixed episodes associated with bipolar I disorder 18+ Schizophrenia	13+ Schizophrenia
Asenapine	18+ Bipolar I disorder	18+ Bipolar I disorder	13+ Schizophrenia 10+ Bipolar disorder 18+ Schizophrenia		18+ Schizophrenia 18+ Manic or mixed episodes associated with bipolar I disorder 18+ Schizophrenia
Ziprasidone	10+ Manic or mixed episodes associated with bipolar I disorder 18+ Schizophrenia	NO	18+ Schizophrenia 18+ Bipolar I disorder		18+ Bipolar I disorder

- 1) Available at: <https://www.hpra.ie>
- 2) Available at: <https://products.mhra.gov.uk/>
- 3) Available at: <https://dailymed.nlm.nih.gov/dailymed/index.cfm>
- 4) Available at: <https://health-products.canada.ca/dpd-bdpp/>
- 5) Available at: <https://www.tga.gov.au/resources/resources>

Brexpiprazole and Cariprazine. Brexpiprazole and cariprazine are both partial agonists at dopamine D2 receptors and antagonists at serotonin 5-HT_{2A}. They are associated with a low risk for both prolactin-elevation and cardiometabolic side-effects albeit not as low as aripiprazole.^{76,78,83} The safety and effectiveness of brexpiprazole and cariprazine has been studied in both adult and adolescent populations although cariprazine has only recently been approved for use in adolescents in the United States only (Table 4). Similar to aripiprazole, brexpiprazole and cariprazine have long half-lives (>91 h and >48 h, respectively) with cariprazine having 2 active metabolites with even longer half-lives (effective half-life for total cariprazine is 1 week).^{90,91}

Asenapine, Lurasidone, and Ziprasidone. Asenapine, lurasidone, and ziprasidone are antagonists at dopamine D2 and serotonin 5-HT_{2A} receptors and have a different pharmacological profile to the partial agonists (aripiprazole, brexpiprazole, and cariprazine). They have shorter half-lives resulting in shorter time-to-effect. Their risk profiles are outlined in Supplementary Material 3. The safety and effectiveness of asenapine, lurasidone, and ziprasidone have been studied in adults. While the safety of both asenapine and ziprasidone has been established in adolescents, the efficacy of these medicines for adolescents with psychotic illness has not been demonstrated (Table 4).^{92–94} Lurasidone, on the other hand, has demonstrated both safety and efficacy in this population in both short and longer-term studies.⁹⁴

Summary

Multiple meta-analyses have examined the risk of both prolactin-elevating and cardiometabolic side-effects with second-generation antipsychotic medicines in adolescents and adults. Based on this information, we have identified 6 medicines that are associated with a low or low-to-medium risk of either/both side-effects in adults and 3 medicines in adolescents. As aripiprazole was the only antipsychotic medicine to show either no change or an improvement, across both prolactin-elevating and cardiometabolic parameters, it should be offered as a first-choice. Brexpiprazole and cariprazine also demonstrated a more favorable profile with regard to prolactin-elevating and cardiometabolic parameters in adults and could therefore be offered as an alternative to aripiprazole. However, cariprazine has only recently been approved for use in individuals under 18 years of age in the United States, and comparative tolerability data in children and adolescents remains limited. As a result, until cariprazine is more widely available, brexpiprazole should be offered to adolescents according to local availability/accessibility/affordability. Lurasidone, asenapine, and ziprasidone, while not completely risk-free, are in the low-to-medium risk category when it comes to susceptibility to cause prolactin-elevating/cardiometabolic side-effects and should be available to adults in whom a

partial agonist is not appropriate with lurasidone only being offered to adolescents.

Practical Considerations in Developing the Algorithm

Half-Life. The D2 partial agonists/5HT_{2A} antagonists (aripiprazole, brexpiprazole, and cariprazine) have longer half-lives which means that time to steady state is approximately 2 weeks. The D2/5HT-2A antagonists, in contrast, have shorter half-lives and result in a shorter time-to-effect. This may be relevant for the choice of antipsychotic in different contexts where time to onset of action is a key consideration.

Dose Escalation. The manufacturers do not differentiate between males and females when it comes to antipsychotic dose initiation and subsequent titration.^{87,90,91,95–98} As females have smaller organs, more fatty tissue and lower blood volume, their volume of distribution is different to males taking the same dose of antipsychotic medicine.⁴⁰ Premenopausal females also have an estimated 10%-15% greater blood flow to the brain, which makes it easier for antipsychotic medicines to reach their target receptors.⁹⁹ The activity of CYP1A2 has been found to be lower in premenopausal females than in males.^{39,100} While this results in wide sex-differences in metabolism of clozapine and olanzapine, it does not affect the medicines we recommend as first-choice options. We examined the evidence on sex-related differences in our Evidence to Decision Framework (Supplementary Material 3) and found the evidence on sex-related changes for aripiprazole of low certainty. However, the manufacturer recommended starting dose of 10 mg was determined to be too high by the GDG. A starting dose of 5 mg for adult females is therefore recommended. This lower starting dose aligns with that recommended in the recently published INTEGRATE guidelines.⁷⁴ Brexpiprazole, cariprazine, and asenapine are understudied and studies on ziprasidone and lurasidone have not been able to demonstrate any sex-related differences.^{101,102} The starting dose and subsequent dose titration for these medicines were therefore not adjusted. The doses and titration schedules are suggestions and may be adjusted according to setting and clinical presentation. The dose may also require adjustment in relation to age/life stage, for example, post-menopause.

Side-Effects. To facilitate the shared decision-making process in the clinical setting, the most common subjectively unpleasant side-effects are described in the algorithm for each medicine in line with the manufacturers' summary of product characteristics.^{87,90,91,95–98}

Pregnancy, Breastfeeding, and Contraceptive Advice. A summary of the details of the available data on the safety of each recommended medicine during pregnancy and while breastfeeding is described in this section of the algorithm along with specific contraceptive advice. Of

note, there are no clinically significant drug–drug interactions between aripiprazole, brexpiprazole, cariprazine, lurasidone, asenapine, ziprasidone, and any oral or other contraceptives.^{87,90,91,95–98,103}

Medicine safety during pregnancy and when breastfeeding are important considerations when treating females of childbearing potential. The evidence base for second-generation antipsychotic medicines in pregnancy and breastfeeding relies largely on observational cohorts, registries, and pharmacovigilance, and is therefore limited. Across recent systematic reviews/meta-analyses, second generation antipsychotic medicines as a class (including aripiprazole, ziprasidone, and lurasidone but not brexpiprazole, cariprazine, or asenapine) are not supported as major teratogens.^{104–106} They appear to carry a low risk of congenital malformations with observational evidence suggesting possible increased risks of preterm birth and neonatal morbidity.^{104–106} However, heterogeneity and residual confounding limits causal inference.

Among the 6 medicines recommended (3 for adolescents), aripiprazole has been studied the most and human data suggests low risk for major congenital malformations, pregnancy loss, or adverse neonatal outcomes above background population risk.^{104–110} There is limited human data of the safety of aripiprazole in breastfeeding but doses of up to 15 mg are reported to produce low levels in milk.¹⁰⁹ As aripiprazole can lower serum prolactin, poor milk supply and lactation cessation have also been reported.¹⁰⁹

Available safety data on lurasidone and ziprasidone is limited and as a result both carry potential risk of adverse pregnancy outcomes.^{104–106,110} Although there is no evidence of teratogenicity with ziprasidone, the manufacturer recommends an “appropriate” method of contraception during treatment.^{97,98} Lurasidone is more than 99% bound to plasma proteins, so it is unlikely that it would be excreted into milk in sufficient amounts to affect a breastfed infant.^{109,110} Nonetheless, data on its safety in breastfeeding is insufficient to make any specific recommendations. As there is little published experience with ziprasidone during breastfeeding potential toxicity cannot be ruled out.^{109,110}

According to a recent systematic review exploring the use of dopamine partial agonists in pregnancy and lactation, there are no formal studies specifically examining brexpiprazole or cariprazine.¹⁰⁷ However, the manufacturers of cariprazine specifically advise against its use during pregnancy or in women of childbearing potential not using effective contraception. Highly effective contraceptive methods are recommended during treatment and for at least 10 weeks following the last dose of cariprazine.⁹¹ There are no formal studies on asenapine safety during pregnancy or breastfeeding.

Overall, medicine-specific risk estimates remain limited for the 6 medicines (3 for adolescents) recommended in this CPG and the “safest” medicines are more often the ones with the most data on their use in pregnancy.

Information Videos. Each antipsychotic medicine recommended in the guideline has a QRcode linking to one of 2 corresponding information videos—one for adults and one for adolescents. The videos were co-designed by pharmacists, psychiatrists, nurses, experts-by-experience, and youth representatives and outline important information associated with the medicine in an accessible way.¹¹¹

Monitoring. As antipsychotic medicines are associated with specific physical health monitoring recommendations, details of the baseline monitoring along with frequency of repeat monitoring is outlined. The monitoring is in line with international recommendations but may be adapted according to the local setting.^{13,75} Those prescribing antipsychotic medicines should play a central role in both monitoring and managing side-effects that negatively impact physical health or subjective experience.⁷⁴ Given that individuals who are antipsychotic-naïve are more susceptible to side-effects, ensuring that baseline and early repeat monitoring is carried out is imperative to ensure early detection and/or preventative interventions. In relation to side-effects that cannot be measured objectively, the use of a validated rating scale is recommended with suggested tools including the GASS (Glasgow antipsychotic side-effects scale)—a 22-question self-rating scale for detecting both frequency and distress associated with second generation antipsychotic side-effects and the BARS (Barnes Akathisia Rating Scale)—a 4-question objectively rated clinical tool designed to assess the presence and severity of akathisia.^{112,113} As sexual side-effects are among the most distressing associated with antipsychotic medicines, exploring these using other relevant assessment tools may be appropriate.⁵⁰

Cautions. Details of potential drug–drug interactions are highlighted, specifically those that prolong QTc interval and those that inhibit or induce the enzymes involved in the metabolism of the recommended antipsychotic medicines CYP2D6 (aripiprazole, brexpiprazole), CYP3A4 (aripiprazole, brexpiprazole, cariprazine, lurasidone), and CYP1A4 (asenapine).^{87,90,91,95–97,103}

Review. Advice on next steps are provided for those who have a good response and good tolerance, those who have good response and poor tolerance and those who have poor response. A recommendation to start planning for clozapine from the time of first presentation is also detailed.

Final Guideline Algorithm

The final guideline algorithm (Fig. 1) outlines the core recommendation to offer 1 of 6 antipsychotic medicines that are associated with a low or low-to-medium risk of prolactin-elevation and/or cardiometabolic side-effects to adults or 1 of 3 antipsychotic medicines to adolescents. Separate versions for adults-only and adolescents-only are also available (Supplementary materials 4 and 5).

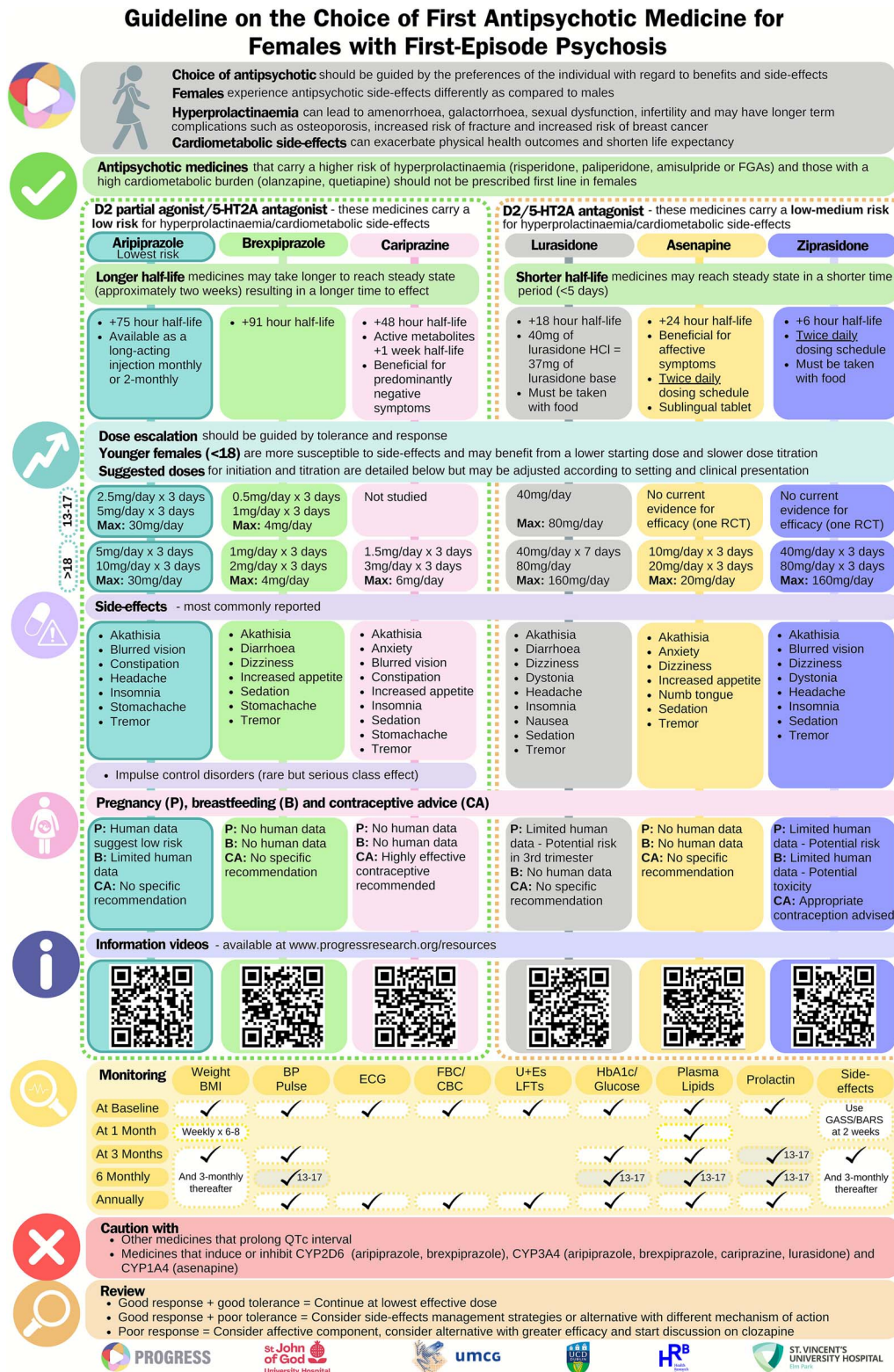


Figure 1. Guideline Algorithm on the Choice of First Antipsychotic Medicine for Females with First-Episode Psychosis.

Results of Field Testing and External Review

Members of the GDG reported that using the guideline algorithm was intuitive, helped with a shared understanding of the decision-making process and supported service user

engagement. The experts-by-experience panel found the guideline flow to be helpful and especially liked the list of most common side-effects and the QR codes to the co-designed medicines information videos. The 2 external

reviewers highlighted that the guideline algorithm may be used differently in different contexts, for example, acute inpatient versus outpatient settings. However, acknowledged that many females experiencing a first-episode of psychosis would be seen first in the outpatient setting.

Update Plan

This is a focused recommendation unit of a suite of guidelines for females. We plan to review and update the guidelines in 3 years.

Discussion

Main Findings

We describe robust methods using GRADE-ADOLOPMENT methodology for the development of a guideline on first-choice antipsychotic medicine for females with first-episode psychosis. We recommend 6 (3 for adolescents) specific agents that are associated with a low/low-to-medium risk of prolactin-elevating and cardiometabolic side-effects for females from age 13+ years. Aripiprazole is selected as first-choice given its low effects on prolactin-related and cardiometabolic side-effects and relative safety during guided gradual tapering.

Clinical Significance

This is the first female-specific CPG on the choice of antipsychotic medicine for adolescent and adult females experiencing first-episode psychosis. Evaluations of the efficacy of antipsychotic medicines have not demonstrated superiority for any individual agent for those experiencing a first-episode of psychosis.^{14,75} The choice of medicine should therefore be guided by a shared decision based on individual preferences, beliefs and values and the treatment options offered by the clinician.^{114,115} Given the number of available antipsychotic medicines, it is not feasible to discuss all options within a single clinical encounter and treatment options must be limited to a manageable subset to support shared decision-making. Real-world prescribing in first-episode psychosis remains concentrated among a limited number of agents, particularly olanzapine.^{26–31} Evidence that olanzapine restriction within guidelines and medicine-specific recommendations improve prescribing quality and outcomes highlight the benefits of greater specificity in CPGs.^{33,34} Females, however, are not specifically accounted for in existing CPGs. Sex-differences in antipsychotic efficacy are insufficiently studied and the available evidence on pharmacokinetic and pharmacodynamic sex differences in our review was of low/very low certainty, precluding their use as reliable determinants of antipsychotic medicine choice at present.³⁸ Additionally, females experience a second peak in first-episode psychosis around the menopausal transition which is characterized by declining estrogen levels and increased vulnerability to bone and cardiometabolic disease. There is an association between prolactin-raising antipsychotic medicines and osteoporosis,

fracture risk, and breast cancer. However, due to the distal relationship between the 2 factors, causality is challenging to demonstrate which is reflected in the certainty of the evidence in our review. Regardless, these potential long-term risks could be reduced by choosing prolactin-sparing medicines. Based on sex-specific physiological differences and subjective experiences of certain side-effects (hyperprolactinemia and cardiometabolic) along with potential negative implications for physical health, the GDG judged that the balance of benefit and harm favors an initial choice of 6 (3 for adolescents) preferred medicines with one medicine of first-choice. This decision is supported by psychological research demonstrating that having too many options to choose from can result in information overwhelm, decreased motivation, an inability to choose, decision-related anxiety, dissatisfaction, and worse outcomes in healthcare.^{116–119} In simplifying the antipsychotic medicine options available, we hope to improve the shared-decision making process for a vulnerable group of antipsychotic-naïve individuals.

Limitations

Effective guideline development and implementation is associated with inherent limitations. This includes the potential biases of the GDG that may influence decision-making. As well as the low certainty evidence on which recommendations may be made. However, we endeavored to adhere to an evidence-based guideline development process according to AGREE II standards and using an Evidence to Decision Framework.

One key limitation associated with implementation of this guideline is the variability in local contexts around antipsychotic medicine licensing and availability. Medicines licensing is the formal process by which regulatory authorities assess and approve a medicine for public use. A medicine receives a marketing authorization (the conditions under which the medicine can be prescribed, including approved indications, dosage, and target population) after rigorous evaluation of its safety, quality, and efficacy, supported by data from clinical trials. The antipsychotic medicines recommended in this guideline are not all licensed in every locality for psychosis from age 13+. Additionally, even where medicines are licensed, they still may not be available as a result of local prescribing restrictions or if the medicine is not marketed in the country in question. However, to overcome this barrier, the GDG has begun the process of engaging with policy makers to improve equity of access to these antipsychotic medicines. Lumateperone (Caplyta®), xanomeline/trospium chloride (Cobenfy®), and cariprazine for adolescents were discussed by the GDG. Due to their absence from comparative studies and availability in only one jurisdiction (United States) they were excluded from the guideline algorithm (cariprazine is recommended for adults only) but may be considered for future versions.

Another barrier to the implementation of this guideline relates to changing prescribing practices of the target users of the guideline. Prescribers may be less familiar with newer

medicines. It is expected that our shared decision-making resources—the guideline algorithm and the medicines information videos—will serve as educational material to both individuals with first-episode psychosis as well as the clinicians caring for them. We also acknowledge that there will be situations where our preferred medicines may not be deemed appropriate and other medicines may be offered. In line with the definition of a “strong recommendation” using the GRADE approach, our recommendations will apply to “most” but not all individuals.⁷⁰ As the purpose of this guideline is not to restrict prescribing but rather to highlight options preferred by “most” individuals, we have also developed shared decision-making resources (medicines information videos) for other medicines including olanzapine, paliperidone, risperidone, and quetiapine—available at www.progressresearch.org/resources.

We make a definitive case for choosing antipsychotic medicines with a lower risk of prolactin-raising and cardiometabolic side-effects for females experiencing first-episode psychosis which reflects a deliberate focus on the critically important patient outcomes. Earlier and established CPGs have primarily focused on neurological side-effects, presenting second-generation antipsychotics as a therapeutic advance on the basis of reduced long-term extrapyramidal risk. We acknowledge that by extending the set of critically important outcomes to include hyperprolactinemia and cardiometabolic side-effects, we assigned lower priority to other side-effects, including anticholinergic and sedative effects. While not deemed to be of critical importance, we appreciate that these outcomes may be important on an individual level. As a result, we have included a list of the most commonly reported side-effects associated with each antipsychotic medicine option in the guideline algorithm. Of note, the 6 medicines recommended (3 for adolescents) are also associated with a lower risk of anticholinergic and sedative effects.

We also acknowledge that while offering antipsychotic medicines with a lower risk of prolactin-elevating and cardiometabolic side-effects, they may not be entirely risk-free. Adolescents are more susceptible to antipsychotic side-effects, especially weight gain, which can even occur with medicines such as aripiprazole.^{77–79} We recommend regular physical health monitoring at baseline and appropriate intervals to ensure that side-effects such as weight gain, should they occur, are identified promptly. Appropriate interventions may then be put in place to mitigate against further risk, for example, initiation of metformin for those who have gained >3% weight at any time during the first year of treatment (adults) or >3% weight outside expected growth trajectory (adolescents).⁷⁷

Finally, as this is a CPG on the first-choice of antipsychotic medicine for females with first-episode psychosis, we have not considered those with affective symptomatology which is a limitation of the guideline. However, certain antipsychotic medicines that we recommend have demonstrated efficacy for both psychotic and manic/affective illness and

are licensed for these indications as outlined in [Table 4](#). These medicines may therefore be preferred for those whose illness has an affective component. We have also included a prompt in the “Review” section of the guideline algorithm to “consider affective component” for those who have had a poor response to their first-choice medicine.

Future Research

This is the first recommendation unit in a suite of guidelines addressing care for females experiencing psychosis across the lifespan. Future research will look at the effective implementation of this guideline and the associated medicines information videos as shared decision-making resources in the clinical setting. The guideline algorithm is an effective tool for shared understanding with service users as it provides a list of (6 for adults, 3 for adolescents) medicines along with the rationale as to why they are being offered. Other clinical supports, such as Psymatik, are also useful in clinical practice to allow clinicians search the latest meta-analytic evidence on side-effects to inform discussions.¹²⁰ Particularly when choosing a second antipsychotic medicine should the individual experience side-effects with the initial choice.

As CPGs support research translation, they are essential in reducing the 17 years it takes for research evidence to reach day-to-day clinical practice.¹²¹ A CPG on the choice of first antipsychotic medicine for males experiencing a first-episode of psychosis is a top priority for future research. Additionally, other CPGs on the pharmacological management of acute agitation and distress for those experiencing psychotic symptoms and a CPG on the management of antipsychotic-induced hyperprolactinemia should also be considered for future guideline development.

Sex-differences in medicine pharmacokinetics and pharmacodynamics are variable and profound, and still have not been thoroughly investigated.¹²² The available evidence on pharmacokinetic and pharmacodynamic sex differences related to the antipsychotic medicines recommended in this CPG is limited ([Supplementary Material 3](#)). Future research should therefore look at the impact of sex differences in first-choice antipsychotic medicine absorption, distribution, metabolism, and excretion as well as the biochemical and physiologic effects of these medicines.

While this is a guideline on first-choice of antipsychotic medicine for first-episode psychosis in females, future guidelines should consider subsequent antipsychotic medicine options for females where a first-choice medicine is ineffective or poorly tolerated. Risperidone, amisulpride, olanzapine, and especially clozapine have demonstrated superior efficacy in those with multi-episode schizophrenia.⁴² However, these medicines carry a higher risk for either prolactin elevation, cardiometabolic side-effects or both. Additionally, strong effects of sex and estrogen have been reported for medicines such as olanzapine and clozapine via CYP1A2 metabolism.^{39,100} As a result, further research on how to optimize these second/third line antipsychotic

medicines in females is crucial to ensure both safety and tolerability.

Conclusion

This guideline represents an important advancement in personalized mental healthcare by providing recommendations for the choice of the initial antipsychotic medicine for females experiencing first-episode psychosis. Developed using a robust and transparent methodology through the GRADE-ADOLOPMENT and AGREE II frameworks, it provides clear, evidence-informed recommendations. While challenges remain in ensuring consistent availability of the recommended medicines—due to differences in licensing, marketing, and prescribing practices—the development group has initiated efforts to address these barriers through policy engagement and clinician education. Future research will focus on the implementation of the guideline and the effectiveness of its accompanying shared decision-making resources, ensuring the recommendations translate into improved patient outcomes and more informed, collaborative prescribing decisions in clinical practice.

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Author Contributions

B. O'Donoghue and I.E. Sommer are joint senior authors.

Supplementary Material

Supplementary material is available at <https://academic.oup.com/schizophreniabulletin>.

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This clinical practice guideline on the choice of first antipsychotic medicine for females experiencing a first-episode of psychosis and the associated algorithm and information videos are made freely available for reference and use in clinical practice. Reproduction and distribution in its original form are permitted without restriction. However, if adaptation, modification, or incorporation into other guidelines, policies, or materials is intended, prior written permission must be obtained from the original authors.

Conflicts of Interest

None declared.

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