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REGULAR ARTICLE

Clinical Practice Guideline on the Pharmacological Management of Antipsychotic-Related Dyslipidemia

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Background: **People taking antipsychotic medicines and those with severe mental illness experience elevated cardiovascular risk compared to the general population which is not adequately addressed by existing guidelines. Increases in lipid levels can occur soon after starting antipsychotics but often go untreated. Cumulative exposure to dyslipidemia from childhood, through young adulthood, facilitates atherogenesis. Regression of early lesions is possible; however, plaque progression can be irreversible, leading to sustained long-term cardiovascular risk. Although lipid-lowering therapies are effective at lowering cardiovascular risk, they are underutilized in this population. We have thus developed a clinical practice guideline for the**

pharmacological management of antipsychotic-related dyslipidemia.
Study Design: **Using GRADE-ADOLOPMENT methodology, an international, multidisciplinary panel including experts-by-experience, developed a guideline for the pharmacological management of antipsychotic-related dyslipidemia. Literature was reviewed to answer key health questions. Patient important outcomes were identified. An evidence-to-decision framework informed the strength of recommendations and external reviews evaluated the rigor of the methods.**
Study Results: **Seven recommendations were developed on how and when to initiate lipid-lowering therapy based on specific criteria including established cardiovascular disease/high-risk conditions, cardiovascular risk assessment, or lipid parameter thresholds. A guideline algorithm illustrates the recommendations alongside supporting prescribing information.**
Conclusions: **This is the first clinical practice guideline for the management of antipsychotic-related dyslipidemia. The inclusion of recommendations for individuals aged 10 years and over represents a significant development. Implementation will be supported by shared decision-making resources including information videos and decision-aids.**

Key words: dyslipidemia; antipsychotic medicine; cardiovascular risk; statins.

Introduction

Dyslipidemia is a common and significant risk factor for the development of atherosclerotic cardiovascular disease and metabolic syndrome.[1,2] It is characterized by increases in total and low-density lipoprotein (LDL-C) cholesterol, low concentrations of high-density lipoprotein (HDL-C) cholesterol, and high triglyceride levels. Chronically elevated LDL-C and low HDL-C levels contribute to reduced arterial elasticity and the development of atherosclerotic plaques.[3,4] Exposure to dyslipidemia in childhood, adolescence, or early adulthood, along with delayed treatment, significantly increases the risk of cardiovascular disease and major cardiac events such as heart attack and stroke in later life.[3,5,6] The risk is cumulative, increasing for every year of delayed treatment.[5] Each 1 mmol/L reduction in LDL-C corresponds with a 20%-25% reduction in the annual rate of major adverse cardiac events.[7] Furthermore, early exposure in youth is associated with a higher risk of cardiovascular disease than exposure later in life.[3,4] Hypertriglyceridemia is also associated with an increased risk of cardiovascular events both independently and via metabolic disturbance.[8-10]

Dyslipidemia is a well-established side-effect of antipsychotic treatment and impacts up to 69% of people with severe mental illness (SMI).[11-13] Clozapine, olanzapine, and quetiapine are associated with the highest risk of dyslipidemia whereas, cariprazine, brexpiprazole, and aripiprazole present a lower risk.[14,15] However, even aripiprazole can cause significant increases in lipid parameters, especially in children and adolescents, indicating that no medicine is risk-free.[15] The pathophysiological mechanisms underlying antipsychotic-related dyslipidemia are multifactorial and include antagonism of histamine H1 and serotonin 5-HT2C receptors, which promotes weight gain and insulin resistance, alongside direct drug-induced disruption of hepatic lipid metabolism and adipogenesis; these effects collectively drive increases in triglycerides, LDL-C, and reductions in HDL-C.[14,16] For those taking antipsychotic medicines, dyslipidemia can occur quickly after initiation and is commonly left untreated.[14,16] Up to 88% of those living with SMI and established dyslipidemia do not receive lipid-lowering treatment which has significant implications for their cardiovascular health.[11,17] Non-pharmacological interventions, such as smoking cessation, diet, and lifestyle strategies, should be offered as standard care to all individuals at the point of initiation of antipsychotic therapy and are endorsed as essential adjunctive therapies to alleviate symptoms, protect physical health, and promote wellbeing in people with severe mental illness or taking antipsychotics.[18-20] However, these alone are unlikely to be effective in mitigating or managing the iatrogenic harm from antipsychotic-related dyslipidemia.

Numerous clinical guidelines for the management of dyslipidemia and prevention of cardiovascular disease have been developed. They recommend the use of cardiovascular risk prediction tools such as SCORE and QRisk3 to guide pharmacological treatment for primary prevention.[8,21] However, people taking antipsychotic medicines have a higher baseline risk of cardiovascular disease which means that traditional risk algorithms underestimate risk in this group—especially for younger adults.[22] Furthermore, risk prediction algorithms do not apply to children, adolescents, or adults under 40 years. Statin therapy has been extensively studied in the general population for its cardioprotective effects and is approved for managing dyslipidemia in adults and familial hypercholesterolemia in children from age 10 years. Statins competitively inhibit HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis, resulting in upregulation of LDL receptors and a subsequent reduction in circulating LDL-C, with additional pleiotropic anti-inflammatory and endothelial-stabilizing effects that may confer particular benefit in the context of antipsychotic-related metabolic dysregulation.[23] While statin therapy is understudied in those with SMI taking antipsychotic medicines, observational data, and subgroup analyses suggest that statin therapy reduces cardiovascular events in this population, with those at higher baseline risk achieving greater absolute benefit.[24,25] Individuals at higher baseline cardiovascular risk also achieve greater benefit from statin therapy for primary prevention of cardiovascular disease.[20] Additionally, statins and high potency omega-3 fish oils [eicosapentaenoic acid (EPA) and docosahexaenoic acid

(DHA)] can lower triglyceride levels.[8-10,26] Omega-3 fatty acids reduce hepatic triglyceride synthesis and enhance clearance via activation of peroxisome proliferator-activated receptors.[27] While direct evidence in the SMI population or among those taking antipsychotic medicines is limited, their established efficacy and favorable tolerability profile support their use in this group.[25,26]

Recent guidelines provide clear recommendations to avoid using medicines with a high risk of cardiometabolic side effects—such as dyslipidemia—as first line agents.[18,28] However, use of medicines with a high risk of dyslipidemia is often necessary for symptom management—for example, the use of clozapine—thus, prescribing higher risk medicines remains widespread.[29-32] Specific guidance is therefore needed to address antipsychotic-related dyslipidemia and support clinicians to intervene promptly to lower cardiovascular risk. The aim of this work was to develop a clinical practice guideline for the first-line pharmacological management of antipsychotic-related dyslipidemia in adults, adolescents, and children aged 10 years and over.

Methods

The GRADE-ADOLOPMENT framework for guideline adaptation was followed and the paper was written with reference to the AGREE II-criteria and the RIGHT-Ad@pt checklist for reporting adapted healthcare guideline recommendations.[33,34] Recommendations were developed from source guidance and evidence syntheses using three strategies: (1) adopt existing recommendations either directly or with minor changes, (2) adapt existing recommendations, making context-specific changes, or (3) develop *de-novo* recommendations to address an absence of recommendations in existing guidelines. Figure 1 outlines a flowchart for the guideline development adapted from the GRADE-ADOLOPMENT methodology. Supplementary Material Chapter 1 details each step of the guideline methodology mapped to the AGREE II criteria.

The Guideline Development Group

An international multidisciplinary team consisting of experts in psychiatry, cardiology, lipidology, general practice, pharmacy, research, endocrinology, and experts-by-experience was convened by invitation. Patient and Public involvement (PPI) was guided by the EVOLVE framework with input from a strategic perspective in topic selection to final review of guideline recommendations.[35] Panel members disclosed potential conflicts of interest which were reviewed by the Guideline Chair (BOD) (Supplementary Material Chapter 6).

Key Health Questions

The key health questions (KHQs) prioritized by the guideline development group (GDG) are outlined below. The panel considered the link between the patient important outcomes of major cardiovascular events and dyslipidemia to be sufficiently established to use dyslipidemia as a surrogate marker.

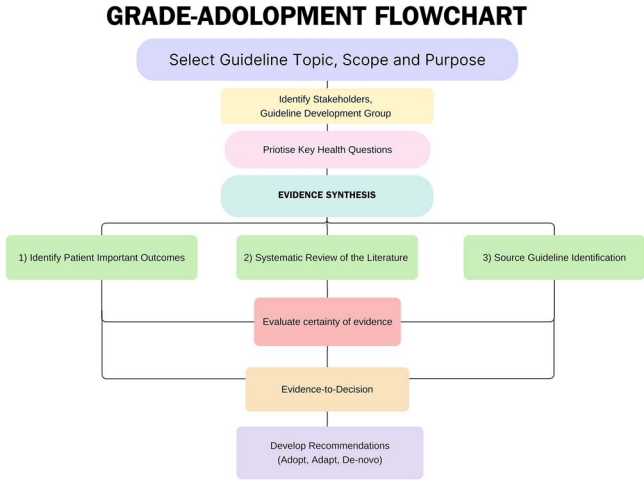

Figure 1. GRADE-ADOLOPMENT Flowchart (Adapted) for the Guideline Development Process.

KHQ 1: What pharmacological interventions are effective for the management of antipsychotic-related dyslipidemia?

KHQ 2: What criteria inform the decision to initiate pharmacotherapy for antipsychotic-related dyslipidemia?

KHQ 3: What thresholds for intervention inform the decision to initiate pharmacotherapy for antipsychotic-related dyslipidemia?

Evidence Syntheses

Work Package 1: Literature Review. Literature was reviewed for 2 populations: (1) children and adolescents, (2) adults. The systematic review search terms, strategy, and results for children and adolescents are available in Supplementary Material Chapter 1. A recently published umbrella review of pharmacological interventions for cardiometabolic outcomes was used for the adult population.[25]

Work Package 2: Source Guideline Identification and Review. A systematic search was conducted to identify clinical practice guidelines for the management of dyslipidemia or cardiovascular disease published up to August 2025 (Supplementary Material Chapter 1—Table 1.2). Titles and abstracts were screened independently by 2 researchers (AC and CHR). Data were extracted using a pre-piloted tool for each of the KHQs by AC and independently checked by CHR. The AGREE-II checklist was applied to each guideline independently by 2 researchers to assess quality and a third researcher resolved any disagreement (AC, DK, and CHR). A guideline was included as a source guideline in the evidence synthesis if it scored 60% or higher on "Domain 3: Rigour of

Development". Where no guidelines existed for the child and adolescent subgroup, consensus statements and guidelines in other populations were collated and the authors of these publications were invited to join the GDG.

Risk of Harm Associated with Statin Treatment

Evidence profiles for important adverse effects of statins were collated from source guidelines. The adverse effects considered were myalgia, myopathy/rhabdomyolysis, liver adverse events, new onset diabetes/dysglycemia, cognitive impairment, hemorrhagic stroke, and other neuropsychiatric adverse effects including anxiety, depression, insomnia, suicidality, and self-harm. Growth and pubertal development were also considered for the child and adolescent group.

Incorporating the Values and Preferences of Experts-by-Experience

A panel of 6 experts-by-experience participated in qualitative interviews to elicit their views on the factors that may influence the decision to initiate pharmacotherapy for antipsychotic-related dyslipidemia. A topic guide consisting of open questions was co-designed with the PPI coordinator (MN).

Development of Guideline Recommendations and Algorithm

An evidence-to-decision framework was developed which informed the direction and strength of each recommendation. A combination of adapted, adopted, and *de-novo* recommendations with panel consensus and a draft algorithm was formed. Field testing in an acute psychiatric hospital setting assessed acceptability and feasibility of the algorithm.

External Reviews

A panel of external reviewers with clinical and research expertise (WC, Jla, JLy, DOS, and JS) were invited to review the guideline development process, recommendations, and algorithm.

Results

Evidence Synthesis

Work Package 1: Literature Review. The systematic review of the literature for children and adolescents (Supplementary Material Chapter 1—Table 1.2), along with the umbrella review for adults found that the evidence for the pharmacological management of antipsychotic-related dyslipidemia remains incomplete. Approved treatments, such as statins and omega-3 fatty acids, have not been studied in individuals <18 years who are taking antipsychotics and very few studies have been conducted in adults ($n = 2$ statins, $n = 4$ omega-3 fatty acids).[25] In these limited adult studies, statins produced consistent and statistically significant reductions in LDL-C and total cholesterol (with variable effects on triglycerides and minimal impact on HDL-C), while omega-3 fatty acids only significantly lowered total cholesterol with no significant improvements in LDL-C, HDL-C, or triglycerides.[36,37] Off-label treatments, for example, metformin, melatonin (<18 s), and topiramate (<18 s) have shown efficacy at lowering certain lipid parameters, although not all.[25]

Work Package 2: Source Guideline Review.

Adult Clinical Guidelines Eight international clinical guidelines were reviewed following screening of a total of 694 titles and abstracts. The review included guidelines from the United Kingdom, Europe, Australia, Canada, and the United States.[8,9,21,38-43] Supplementary Material Chapter 2—Table 2.3 lists excluded guidelines and reasons for exclusion. Guidelines targeted specifically at those with SMI were reviewed but ultimately excluded because these guidelines adopted recommendations from already included guidelines without adaptation.[18,44-47] Supplementary Material Chapter 2—Table 2.4 describes AGREE-II assessment results for the included guidelines. One guideline was excluded after application of AGREE-II for scoring less than 60% in "Domain 3: Rigour of Development." Seven adult guidelines were included in the evidence synthesis as source guidelines.

Child and Adolescent Clinical Practice Guidelines For children and adolescents, there are currently no clinical practice guidelines for the use of statins in those without familial hypercholesterolemia. As a result, the GDG considered evidence from populations at elevated risk of cardiovascular disease. One clinical practice guideline, 1 consensus statement, and 1 clinical practice update were included in the evidence synthesis for children and adolescents.[6,48,49] Table 1 summarizes the results of the evidence synthesis for each KHQ.

Risk of Harm from Statin Therapy

Supplementary Material Chapter 3—Table 3.1 details the evidence-to-decision framework and evidence profiles. The risk of muscle pain, tenderness or weakness (myalgia), and the rate of severe muscle adverse effects (rhabdomyolysis) associated with statin use is extremely low.[21] Myopathy occurs in rare cases (approximately 1 in 10 000 people/year) and rhabdomyolysis (as indicated by muscle symptoms and multi-fold rises in creatine kinase) has approximately 2-3 cases per 100 000 people/year.[50] In addition, statin therapy causes a small absolute increase (about 1%) in less severe muscle symptoms, although this excess is largely confined to the first year of treatment.[50] The updated clinical review for NICE 2023 found a small increase in diabetes that did not meet the criteria for clinically important harm.[51] Evidence of neuropsychiatric adverse events is limited to cohort studies (low certainty evidence) but overall, there is no evidence that statin therapy increases the risk of neuropsychiatric adverse events. For children and adolescents, no abnormalities in growth or puberty were demonstrated.[52]

Table 1. Summary of Comparison of Guideline Recommendations for Key Health Questions (KHQs)

KHQ1	What pharmacological interventions are effective for the management of antipsychotic-related dyslipidemia?	All adult source guidelines agreed that there is sufficient evidence to recommend statin therapy for the primary prevention of cardiovascular disease in adults in the general population based on specific criteria or risk assessments. Guidelines agreed on the benefit of lipid lowering interventions in protecting against major adverse cardiac events and almost all guidelines refer to the 2010 Cholesterol Treatment Trialists Collaboration finding that a 1 mmol reduction in LDL is associated with an approximate 20% reduction in the annual risk of major adverse cardiac events.[7] Source guidelines for children and adolescents recommend statin therapy for the management of elevated LDL-C. Evidence profiles for statin therapy were developed from the source guidelines and are detailed in Supplementary Material Chapter 3.
KHQ2	What criteria inform the decision to initiate pharmacotherapy for antipsychotic-related dyslipidemia?	Most adult guidelines have recommendations for the initiation of statin therapy in those with existing cardiovascular disease, chronic kidney disease, diabetes and established familial hypercholesterolemia but differences exist in the exact criteria within these conditions. Supplementary Material Chapter 4—Table 4.1 outlines the differences in recommendations, definitions and criteria. All adult guidelines recommended the initiation of statin therapy for primary prevention based on a cardiovascular risk assessment. Some adult guidelines also recommend primary prevention based on lipid parameters. Where guidelines referred to severe mental illness, they identify higher risk in this population but do not make specific adjustments to recommendations or guide management of antipsychotic-related dyslipidemia. Child and adolescent guidelines recommend statin therapy at defined LDL-C thresholds depending on specific co-morbidities. Supplementary Material Chapter 4—Tables 4.1 and 4.2 outline the recommendations contained within the included guidelines regarding the parameters or clinical characteristics that inform the decision to start statin therapy.
KHQ3	What thresholds for intervention inform the decision to initiate pharmacotherapy for antipsychotic-related dyslipidemia?	The threshold for starting a statin in most source guidelines is a cardiovascular risk score of 10% or higher, but some guidelines allow clinical interpretation and the initiation of a statin at lower cardiovascular risk scores.[19,39,43] Where source guidelines made specific recommendations for statin therapy based on lipid parameters, LDL-C and total cholesterol (TC) were usually referenced. Of note, NICE 2023 and Canada 2021 guidelines gave thresholds for non-HDL cholesterol.[22,40] Other parameters such as apolipoprotein B and lipoprotein (a) are referenced in most guidelines, but only Canada 2021 guidelines give thresholds for statin initiation based on these parameters.[40] Many guidelines allow statin initiation at slightly lower lipid thresholds in the presence of additional risk factors with subtle differences in the criteria for these additional risk factors. Source guidelines for children and adolescents categorize pediatric patients as very high-risk, high-risk, moderate-risk or at-risk based on the presence of co-morbidities. Intervention thresholds with statin therapy for LDL-C depend on the risk category.[6,48,49] Intervention thresholds across each of the source guidelines were extracted and are presented in Supplementary Material Chapter 4—Tables 4.1 and 4.2.

Views and Preferences of Experts-by-Experience

A content analysis of qualitative feedback identified four factors that would influence an individual's decision regarding pharmacological treatment of dyslipidemia (Table 2). Evidence on preferences and values from the general population was also considered in the evidence-to-decision framework (Supplementary Material Chapter 3).

Developing Recommendations

The GDG held a series of meetings to incorporate stakeholder views and reach consensus on guideline recommendations. The evidence-to-decision framework and detailed explanation for each judgment are provided in Supplementary Material Chapters 3. Key discussions focused on managing iatrogenic harm and the use of statins in children and adolescents. The GDG agreed that antipsychotic-related dyslipidemia requires a novel approach, as existing guidelines do not adequately account for the elevated cardiovascular risk of those taking antipsychotic medicines or living with SMI—risk that is underestimated by traditional assessment tools. Accordingly, lower intervention thresholds were considered appropriate. The GDG also noted that dyslipidemia beginning in childhood warrants thresholds independent of cardiovascular risk assessment. Given the limited evidence for non-pharmacological strategies to address iatrogenic harm, the GDG supported a more proactive approach with earlier consideration of pharmacological interventions.

While statin therapy for individuals aged 10-17 years without familial hypercholesterolemia is unlicensed (ie, it does not have official approval from national regulatory authorities), the iatrogenic harm from antipsychotic-related dyslipidemia warrants intervention with a combination of

Table 2. Preferences of Experts-by-Experience

Factor/outcome	Description	Quote
Age	Participants described associating statins with older populations and some reluctance to initiate statins at a young age.	"For me it's my age. I'm kind of like only XX (years). Why am I taking a statin? . . . when you think of statins you think about heart attacks . . . it's like that's for old people." (Participant B)
Lipid Parameters	Elevated lipid parameters would drive the decision to take a statin rather than the risk of cardiovascular events.	"The figure for cholesterol of the bad cholesterol and the good cholesterol would be important ...." (Participant D)
	Short term outcomes were prioritized over longer-term outcomes such as the risk of heart attack/stroke	"Those all seem very far out to me, so I'd be hoping that, you know, the improvements would start straight away..." (Participant C)
Polypharmacy	Polypharmacy was identified as a factor that may deter people from starting pharmacotherapy for antipsychotic-related dyslipidemia	"Naturally, I'm also conscious of the fact of the amount of medication I'm already taking." (Participant B)
Shared decision-making	Provision of clear information on the benefits and risks of statins is an important factor in the decision to start pharmacotherapy for antipsychotic-related dyslipidemia.	"A really solid presentation of what the risks are if you didn't take the statin (would inform the decision to take a statin)." (Participant C)

Table 3. GRADE—Grades of Recommendation, Assessment, Development, and Evaluation[33]

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.

diet, lifestyle, and pharmacotherapy. Defining baseline risk in this population was difficult due to uncertainty around the underlying pathophysiology of antipsychotic-related dyslipidemia. The GDG agreed on new recommendations for individuals aged 10-17 years using thresholds and co-morbidity definitions adapted from the source documents.[6,49] Due to the absence of high certainty evidence, this is a conditional recommendation (Table 3).

High dose omega-3 fatty acids are effective at reducing triglyceride levels.[8] The supplements are difficult to tolerate and often not funded by state schemes, incurring a cost to individuals. However, antipsychotics can frequently cause triglyceride elevation independent of increased LDL-C. The GDG decided therefore, as a conditional recommendation, that individuals should be offered high dose omega-3 fatty acids when triglyceride levels are elevated but do not meet the threshold for statin use.

Core Recommendations. Seven core recommendations were developed with a more detailed description including the method, source, strength, direction, and justification for each recommendation in Supplementary Material Chapter 5—Tables 5.1-5.7.

> **Recommendation 1:** *We recommend statin therapy irrespective of lipid parameters or cardiovascular risk score in the following groups: Established cardiovascular disease, Chronic kidney disease (eGFR < 60 mL/min), Diabetes aged > 40 years, Diabetes with duration ≥ 20 years, Adults with T1DM with duration ≥ 10 years and Established familial hypercholesterolemia.*
> *(Strong recommendation in favor—adopted from existing guidelines)*

Recommendation 2: *We recommend statin therapy for adults LDL-C ≥ 3.0 mmol/L or triglyceride ≥ 2.4 mmol/L (fasting).*
(Strong recommendation in favor—adapted from existing guidelines)

Recommendation 3: *We recommend statin therapy for adults aged 18 years or over with a 10-year CV risk score of 10% or higher.*
(Strong recommendation in favor—adopted from existing guidelines)

Recommendation 4: *We suggest statin therapy for adults aged 18 years or over with a 10-year CV risk score of >5%.*
(Conditional recommendation in favor—adapted from existing guidelines)

Recommendation 5: *We suggest statin therapy for* antipsychotic-related *dyslipidemia in people aged 10-17 years with LDL ≥ 4.0 mmol/L that has been confirmed on at least 2 laboratory samples, one to be fasting, after a 3-month watch and wait period. (Note: unlicensed indication for statin therapy in this age group).*
(Conditional recommendation in favor—De novo)

Recommendation 6: *We suggest statin therapy for* antipsychotic-related *dyslipidemia in people aged 10-17 years with LDL ≥ 3.4 mmol/L that has been confirmed on at least 2 laboratory samples, one to be fasting, and the presence of one or more risk-enhancing co-morbidities, after a 3-month watch and wait period. (Note: unlicensed indication for statin therapy in this age group).*
(Conditional recommendation in favor—De novo)

Recommendation 7: *We suggest high-dose omega-3 fatty acid supplements (with at least 2 EPA: 1 DHA) in adults and young people (aged 10 years and over) who do not meet criteria for a statin if triglyceride ≥ 1.7 mmol/L (fasting).*
(Conditional recommendation in favor—De novo)

Algorithm Development

The algorithm (Figure 2) was developed to incorporate the core recommendations, good practice recommendations, referral criteria, and key prescribing information.

Good Practice Recommendations. Diet and lifestyle interventions are recommended as standard care at initiation of antipsychotic therapy to improve multiple mental and physical health outcomes. While the iatrogenic effects of antipsychotic medicines on lipid parameters are unlikely to be effectively mitigated by these interventions alone, they have demonstrated promise at reducing weight and improving additional cardiovascular health parameters and are endorsed as essential adjunctive therapies to alleviate symptoms, protect physical health, and promote wellbeing in those taking antipsychotic medicines or living with SMI.[20,53] For adults, this means offering and continuing intensive diet and lifestyle interventions from the outset. For individuals aged 10-17 years, intensive diet and lifestyle interventions are recommended during the 3-month watch and wait period following identification of dyslipidemia. Such interventions should be continued in both populations if pharmacotherapy is initiated.

Measuring Lipid Parameters. The need for fasting samples was considered by the GDG. All adult source guidelines recommend assessing non-fasting lipid levels. The Va/DOD guidelines advise that fasting lipid levels add no clinical value to risk prediction compared to non-fasting levels but are considerably more burdensome for patients and more costly.[43] However, hypertriglyceridemia should be interpreted with caution as non-fasting samples display a higher triglyceride level of ~0.3 mmol/L.[8] Pediatric source guidelines recommend that abnormal lipid parameters are confirmed with at least one repeat sample that is fasting and at least 2 weeks but no less than 3 months after the initial finding.[6,48,49] Responsibility for lipid monitoring and management should be explicitly agreed and documented prior to initiating antipsychotic therapy; this will depend on local service agreements within mental health settings and may vary between jurisdictions.

Choice and Dose of Statin. A moderate-intensity statin (atorvastatin 10-20 mg) is recommended because of experience with its use in adult and pediatric populations. Furthermore, atorvastatin's relatively long half-life (approximately 14 h) allows for flexible dosing at any time of day, thereby facilitating concurrent administration with antipsychotic medicine with potential improvement in treatment adherence. Moderate-intensity statins reduce LDL-C by about 30% on average in adults and 40% in children and adolescents.[8,54] A starting dose of 10 mg for children and adolescents and 20 mg for adults is recommended with the option to increase the dose to 20 and 40 mg, respectively, if treatment targets are not reached after 4-8 weeks.[21,55] Statins produce a log-linear dose–response, therefore, effectiveness does not increase proportionally with dose and approximately two-thirds of the expected maximum response usually occurs with 25% of the highest dose.[55,56] While atorvastatin is recommended as a first-choice, alternative moderate intensity statins may be considered based on individual clinical need and local availability, including rosuvastatin (starting at 5 mg for children and adolescents and 10 mg for adults with the option to increase the dose to 10 and 20 mg, respectively). If lipid targets are not reached at 3-6 months at the highest tolerated statin dose, referral to GP or cardiologist is recommended.

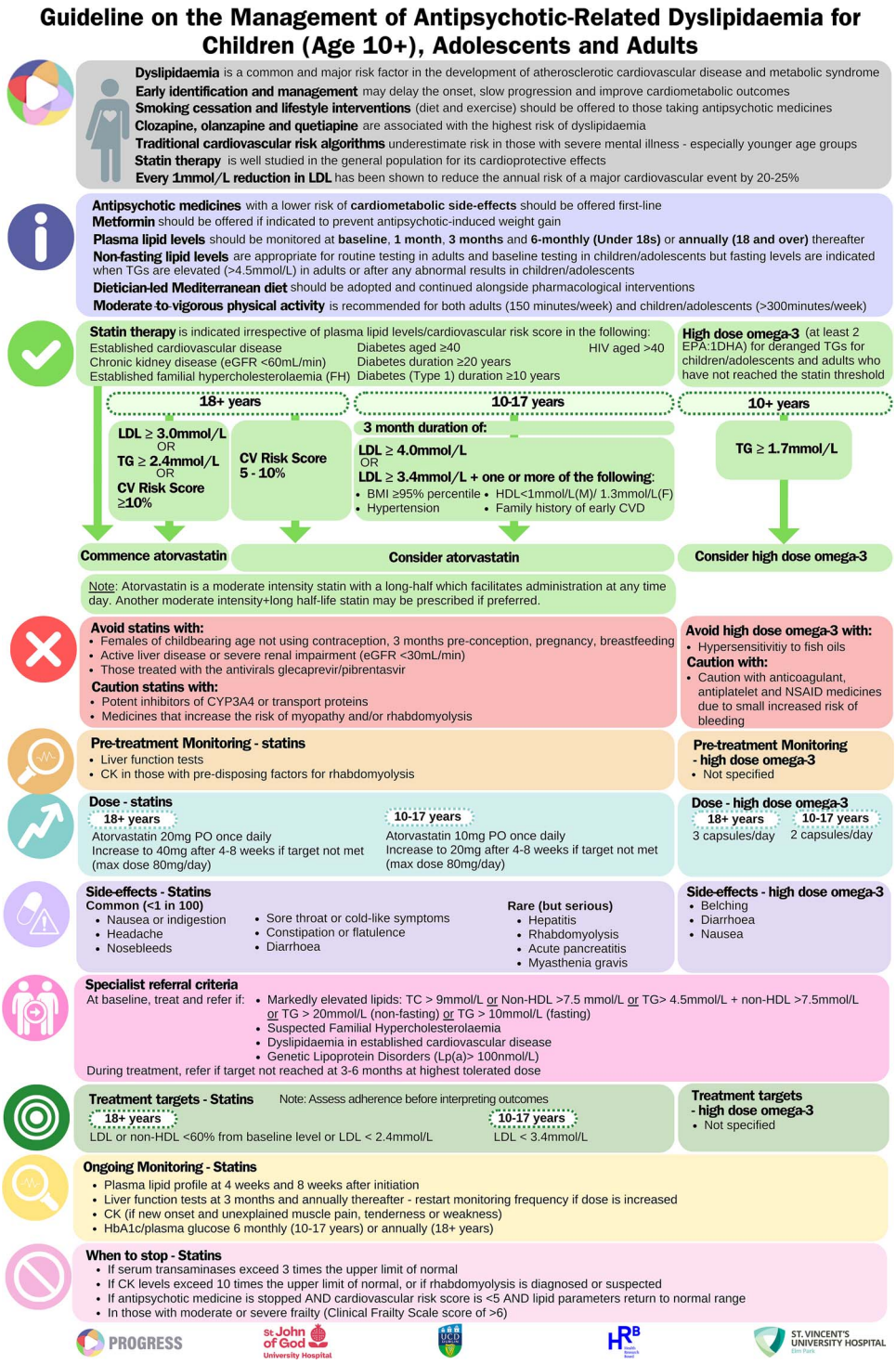

Figure 2. Guideline Algorithm on the Pharmacological Management of Antipsychotic-Related Dyslipidemia.

Contraindications, Cautions, and Drug–Drug Interactions. Atorvastatin is contraindicated during pregnancy. We have therefore included a recommendation to avoid atorvastatin in females of child-bearing potential not using contraception, for 3 months pre-conception, during pregnancy and breastfeeding.[56] Atorvastatin is also contraindicated in those with active liver disease, severe renal impairment or treated with the antivirals glecaprevir/pibrentasvir.[56] High-dose omega-3 is contraindicated in those with a hypersensitivity to fish oils. There are no clinically significant drug–drug interactions between atorvastatin, high dose omega-3 fish oils and antipsychotic

medicines.[57] However, caution is advised when atorvastatin is prescribed for those also taking potent inhibitors of CYP3A4 or transport proteins or other medicines known to increase the risk of myopathy and/or rhabdomyolysis. High-dose omega-3 should also be prescribed with caution for those taking anticoagulant, antiplatelet, and NSAID medicines due to small increased risk of bleeding.[58]

Baseline and Ongoing Monitoring Recommendations. In line with the manufacturers of atorvastatin, we recommend baseline liver function tests and creatine kinase levels for those with pre-disposing factors for rhabdomyolysis including renal impairment, hypothyroidism, personal or familial history of hereditary muscular disorders, previous history of muscular toxicity with a statin or fibrate, previous history of liver disease and/or where substantial quantities of alcohol are consumed, situations where an increase in plasma levels may occur and special populations including genetic subpopulations.[56] Repeat liver function tests are indicated 3 months after statin initiation and annually thereafter and repeat creatine kinase levels only if new onset and unexplained muscle pain, tenderness, or weakness presents. Follow-up plasma lipid levels are recommended at 4 and 8 weeks to guide statin dose titration. There are no specific baseline or ongoing monitoring recommendations associated with high-dose omega 3. HbA1c/plasma glucose monitoring is indicated 6-monthly for children and adolescents and annually for adults in line with international physical health monitoring guidelines for those prescribed antipsychotic medicines.[59-61]

Discussion

Main Findings

New clinical practice guidelines for managing antipsychotic-related dyslipidemia have been developed using GRADE-ADOLOPMENT methodology and AGREE-II criteria to adhere to standards for high quality guidelines.[62] A systematic review of pharmacological interventions for antipsychotic-related dyslipidemia revealed a lack of evidence. Additionally, a systematic review of existing clinical practice guidelines for managing dyslipidemia or cardiovascular risk was conducted. Where source guideline recommendations applied equally to our population, these were adopted without change. Where recommendations were relevant but not specific to those with antipsychotic-related dyslipidemia, these were adapted to account for elevated cardiovascular risk. Where there were no existing recommendations, de-novo recommendations were created using an evidence-to-decision framework. The guideline contains recommendations to initiate lipid lowering therapy based on pre-existing indications, high risk conditions, lipid parameters, or cardiovascular risk scores. They are stratified according to age to include recommendations for individuals aged 10 years and over. This approach is particularly relevant given that individuals taking antipsychotic medicines or those living with SMI are at higher baseline risk of cardiovascular disease even without antipsychotic therapy, further motivating uptake of this clinical practice guideline. An algorithm (Figure 2) illustrates the seven recommendations alongside key prescribing information and good practice recommendations.

Dyslipidemia is one of several cardiometabolic side-effects associated with antipsychotic treatment, often occurring alongside antipsychotic-induced weight gain and obesity. This clinical practice guideline on antipsychotic-related dyslipidemia complements two related clinical practice guidelines from our PROGRESS research group: one on the choice of first antipsychotic medicine for females with first-episode psychosis, which recommends offering medicines with low or low-medium risk of cardiometabolic (and prolactin-elevating) side-effects first-line; and another on metformin for the prevention of antipsychotic-induced weight gain, which recommends co-commencement of metformin with specific antipsychotic medicines and/or in the presence of certain comorbidities.[28,63] Clinicians should therefore refer to these complementary guidelines to support proactive selection of lower-metabolic-risk antipsychotic medicines and preventive strategies during antipsychotic initiation or continuation. Together, these resources provide a comprehensive framework for mitigating cardiometabolic risks—including dyslipidemia—in those prescribed antipsychotic medicines.

Clinical Significance

The underlying pathophysiology of dyslipidemia in those taking antipsychotic medicines and the onset of metabolic dysfunction in this population is not fully understood. However, chronic exposure to elevated LDL-C and triglycerides can lead to plaque formation which increases the risk of cardiovascular disease later in life. Until now, individuals taking antipsychotic medicines had been underserved by existing guidelines for the management of dyslipidemia and prevention of cardiovascular disease. In particular, the absence of clear recommendations for the use of lipid lowering therapies for young adults and those aged 10-17 years means that dyslipidemia is often left untreated. This guideline provides a framework for clinicians and individuals living with antipsychotic-related dyslipidemia to discuss the option of lipid lowering therapy and make informed decisions about whether to start pharmacotherapy according to specific criteria. New recommendations advocate for the use of statin therapy to manage antipsychotic-related dyslipidemia in individuals aged 10-17 years. This reflects the consensus opinion of the GDG that, on balance, the evidence favors the intervention at defined LDL-C thresholds. Statins are approved for children as young as eight years for familial hypercholesterolemia and have therefore demonstrated safety in this population where the cardiovascular risk is sufficient to warrant intervention.[54]

This guideline does not recommend a specific cardiovascular risk assessment tool. Instead, it refers to the available

risk assessment tools to facilitate local choice. Traditional cardiovascular risk algorithms (QRISK3, QDiabetes) underestimate risk in people taking antipsychotic medicines and those living with SMI (Hughes et al. in press).[11,64-67] The mechanism of dyslipidemia in those taking antipsychotic medicines and those with SMI is likely multifactorial and driven by a cluster of factors including metabolic syndrome, abdominal obesity, and insulin resistance. SMI-specific risk prediction models for cardiometabolic risk such as PsyMetRIC use triglyceride and HDL-C parameters in the risk prediction algorithm because these lipid parameters predict insulin resistance.[64] A validated threshold for intervention based on the outcome of the PsyMetRiC tool could allow inclusion of this risk prediction model in future iterations of this guideline.

The scope of this guideline is to support clinicians in psychiatry and general practice to initiate first-line treatment for antipsychotic-related dyslipidemia. Second-line pharmacological interventions were excluded from the evidence synthesis. Such interventions include ezetimibe, fibrates, and more intensive treatments like proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, icosapent ethyl, and bempedoic acid. Where statins are not tolerated or not optimally effective, referral criteria are outlined in the algorithm to allow specialist intervention and consideration of additional pharmacological interventions as indicated. Additionally, metformin and antipsychotic switching were not considered in this guideline (due to scope limitations on licensed first-line treatments), though metformin shows promise for reducing total cholesterol and triglycerides in adults, and LDL-C in children/adolescents taking antipsychotic medicines.[25,36] While Kanagasundaram et al. found "approved lipid-lowering agents" to be less effective than switching or metformin, it is important to note that only one of the five studies in this meta-analysis examined statin therapy with the remaining four investigating omega-3 fatty acids. A more recent systematic review by Ferrell et al. specifically examined statin therapies in individuals taking antipsychotic medicines (6 studies, $n = 333$ patients) and found that statins appear effective for managing antipsychotic-related dyslipidemia, particularly through significant reductions in LDL-C (observed in all five studies with statistical testing).[37] Although metformin exhibits promising efficacy in the management of antipsychotic-related dyslipidemia, antipsychotic switching may not be feasible for those already receiving low-risk agents or those requiring higher-risk medicines due to inadequate response or poor tolerability to lower-risk alternatives.

Non-pharmacological interventions are widely recommended as standard care for the management of dyslipidemia and prevention of cardiovascular disease. In source guidelines for adults, these interventions serve as initial steps for low-risk patients and can be combined with pharmacological interventions. Lifestyle and dietary interventions are also likely to improve mental health outcomes.[68] The GDG recommends that non-pharmacological interventions should be offered to individuals taking antipsychotic medicines at initiation and continued alongside statin/high-dose omega-3 therapy. As antipsychotic-related dyslipidemia is iatrogenic, diet and lifestyle interventions are unlikely to be sufficient to treat it. Additionally, if individuals prescribed antipsychotic medicines are offered diet and lifestyle interventions at the point of initiation, and later develop dyslipidemia, this suggests such interventions have not been effective in preventing dyslipidemia and therefore, are unlikely to be effective at managing it.

An additional clinical consideration relating to our guideline recommendations (6 and 7) is the feasibility of offering high-dose omega-3 therapy in routine clinical practice. While atorvastatin is inexpensive and widely available, high-dose omega-3 preparations can be costly and are often not reimbursed under community drug schemes. In addition, product quality and regulatory status may vary as only some formulations are licensed medicinal products while others are marketed as food supplements. These factors may impact equitable access and real-world uptake, particularly in health systems where out-of-pocket cost influences treatment decisions. This should be considered when interpreting the applicability of the recommendations to offer high-dose omega-3 for deranged triglycerides.

Limitations

Guideline development methodology is associated with inherent limitations. For example, bias within the GDG can influence the content and strength of recommendations. However, by including a wide range of disciplines, managing conflicts of interest, including multiple external reviewers and numerous rounds of consultation, we have endeavored to limit potential bias. The strength of recommendations is largely determined by the certainty of evidence for a course of action. There was a limited evidence base to inform recommendations specifically for antipsychotic-related dyslipidemia. In the absence of high certainty evidence, a GDG must make judgments to answer KHQs that are important in clinical practice. GRADE-ADOLOPMENT and the use of an evidence-to-decision framework provides a transparent way to move from evidence to recommendation.

Implementation and Future Research

Clinicians working in psychiatry may be unfamiliar with prescribing statins and the application of cardiovascular risk prediction tools. Time constraints are also a barrier to applying risk prediction tools across clinical settings. A simplified algorithm, with clear recommendations drawn from recent international clinical practice guidelines, will support implementation. Additionally, the use of LDL-C thresholds will reduce the frequency of need for complex risk prediction calculations.

Consultation with experts-by-experience highlighted common barriers to implementing statin therapy for primary prevention such as low perceived risk of future

cardiovascular disease and preference to avoid increased pill burden. Implementation of this clinical practice guideline will be supported by shared decision-making tools including co-designed information videos. The importance of shared decision-making was also emphasized in the source guidance.[21,38,42]

Future research should include refining risk prediction models to address the needs of individuals with SMI and/or antipsychotic-related dyslipidemia. Patient, clinician, and system level barriers and facilitators to implementation require exploration. The effectiveness of the guideline will be investigated to assess whether implementation leads to improved monitoring of lipid levels, earlier detection and management of dyslipidemia.

Finally, sex differences represent an important understudied area in antipsychotic-related dyslipidemia. Evidence from existing systematic reviews remains limited and frequently underpowered to detect sex-specific effects on lipid parameters (eg, triglycerides, LDL-C, HDL-C). Future research should prioritize adequately powered trials and subgroup analyses stratified by sex to clarify these differences, improve personalized treatment approaches, and address potential inequities in cardiometabolic risk management among individuals taking antipsychotic medicines or living with SMI.

Conclusion

This is the first clinical practice guideline for the management of antipsychotic-related dyslipidemia and the inclusion of specific recommendations for individuals aged 10-17 years represents a significant development. Through implementation of this guideline, individuals who experience antipsychotic-related dyslipidemia and meet specific criteria will now have the option to start lipid lowering pharmacotherapy to reduce cardiovascular risk. Implementation of this guideline will be supported by shared decision-making tools including patient information videos and decision-aids.

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Author Contributions

Aoife Carolan and Caroline Hynes-Ryan are joint first authors. AC, CHR, DK and BOD were part of the steering group who conceived the project. AC, CHR, and HT conducted the literature reviews. AC, CHR and DK extracted and checked data, prepared evidence tables, contributed to the development of the evidence profiles, applied AGREE II criteria and applied GRADE-ADOLOPMENT framework to the source guidelines selected. BOD chaired the Guideline Development Group and DK supervised the methodological approach. MN led the patient and public involvement processes and co-designed the qualitative topic guide. MN, RB, SMH and ES provided lived experience input from a strategic perspective in topic selection, guideline iteration and final review of guideline recommendations. DC, SdF, IK, CK, MK, JLy, Jla, KOC, POC, BP, TP, DSh and DSi contributed to drafting and revising the guideline recommendations, participated in consensus meetings and critically reviewed the manuscript. DOS, WC, CR and JS carried out an external review of the guideline and reviewed the final guideline. All authors had full access to the data in the guideline development process, take responsibility for the decision to submit the manuscript for publication and have approved the final version.

Supplementary Material

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

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