INTEGRATE: international guidelines for the algorithmic treatment of schizophrenia

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Schizophrenia is a mental illness involving multiple symptom domains and is often associated with substantial physical health comorbidities. Guidelines exist, but these tend to be country-specific and are often missing a concise yet comprehensive algorithmic approach. From May 1, 2023, to Jan 1, 2025, International Guidelines for Algorithmic Treatment (INTEGRATE) authors from all UN regions collaborated to develop a consensus guideline focused on the pharmacological treatment of schizophrenia. Following an umbrella review of the literature, input from expert workshops, a consensus survey, and lived experience focus groups, a consensus algorithmic guideline and associated digital tool were developed. Key recommendations include a focus on metabolic health from treatment initiation, timely assessment and management of non-response, symptom domain-specific interventions, mitigation of side-effects, and the prompt use of clozapine in cases of treatment resistance.

Introduction

Schizophrenia affects approximately 0·7% of the global population during their lifetime, including 0·32% of the population at any one time, and imposes a significant health-care burden worldwide.[1–4] Effective treatments exist; however, pharmacological treatments are often associated with substantial side-effect burden and delays in providing optimal treatment are common.[5–7]

Numerous guidelines exist regarding the treatment of schizophrenia.[8,9] Although they provide evidence-based guidance, these guidelines are often lengthy, country-specific, and are often missing a structured, algorithmic approach, which can make them less practical in clinical settings. Where algorithmic advice is given, this advice might not be sufficiently specific. A 2022 review highlighted these shortcomings, and also noted inadequate guidance on maintenance treatment duration and management of negative symptoms in particular.[10]

In response, we collaborated with experts from 30 countries across all UN regions to develop a globally relevant, concise, algorithmic, and evidence-based guideline for the treatment of schizophrenia.

Guideline development

Initial discussions about the need for an algorithmic international guideline occurred at the Schizophrenia International Research Society Meeting (SIRS) in May 2023.

Umbrella review

Between July 21 and September 30, 2023, an umbrella review (PROSPERO CRD42023446098) was undertaken (see appendix pp 2–8 for full protocol) to inform the questionnaire.

Survey and guidelines drafting

A draft questionnaire informed by the umbrella review was iteratively refined by the core steering committee and a focus group of individuals with lived experience of schizophrenia between Oct 1, 2023, and Jan 31, 2024. Focus groups included individuals with both first-episode and more established illness, and were diverse in terms of ethnicities, gender, and age. Although psychological and social interventions are important components in the management of schizophrenia during all phases of illness, this guideline development focused primarily on pharmacological treatment and side-effect management.

The initial survey, completed by the Treatment Response and Resistance in Psychosis working group between Feb 1 and Mar 31, 2024, had 70 respondents from 30 countries representing all UN regions. Statements endorsed by over 70% of respondents were incorporated into the guideline. Based on these responses, an initial treatment algorithm was developed and presented at an SIRS workshop in April, 2024, which was attended by 255 individuals. Feedback from the workshop informed a second survey conducted between Apr 30 and May 24, 2024, on relevant steps where consensus was not reached, or clarification was needed. The initial guideline draft was created in May and June, 2024, then reviewed by a lived experience focus group, followed by the working group again from June to August, 2024.

Guideline recommendations

General principles

Shared decision making

Shared decision making involving the person diagnosed with schizophrenia and their carers should be done whenever possible. At the earliest possible time during the treatment course, individuals with schizophrenia should be involved in decisions regarding their treatment.[9,11–15] They should be informed about the range of treatment options available, including psychosocial interventions, the potential risks and benefits of different treatment options, and the value of giving ongoing feedback on treatment progress.

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See Online for appendix

Individualised treatment

Treatment should be individualised based on current symptoms and patient preferences regarding side-effects, efficacy, and route of administration.[9,11–15] Care should be taken to account for factors that might affect pharmacokinetics and thereby dosing. These factors include age, gender, ethnicity, comorbidities (eg, hepatic or renal impairment), concomitant medications, tobacco use, caffeine use, and adherence to manufacturer instructions as to whether dosing should occur with or without food.[16–19] If available, plasma medication concentrations should be used to inform dosing in specific populations.[16,17] Some medications (eg, cariprazine) require the use of effective contraception if prescribed to female patients of childbearing age.

The cost and availability of treatments could also determine which options can be considered. In some settings, for example, only a single antipsychotic might be available. In this case, some general principles of the guidelines still apply—to attempt to engage patients in decision making, to use the lowest effective dose, and to address side-effects promptly. In cases of inadequate response and no alternative antipsychotics being available, a decision might need to be made as to the benefits of continued treatment. The current guideline aims to give greater specificity in terms of drug choices, with the result that, at times, recommended treatments might not be available. In this case, tools to weigh up the relative side-effects of a full range of antipsychotics can be considered.[20–22]

Act early

Treatment effectiveness should be assessed early, and a proactive approach used when commencing, switching, or augmenting treatment because of inadequate efficacy or poor tolerability.[23]

First-episode psychosis

Initial treatment

At the first presentation of psychosis, treatment might need to be initiated before a diagnosis of schizophrenia has been unequivocally established. Antipsychotic treatment should be offered to individuals who have experienced a week or more of psychotic symptoms with associated distress or functional impairment.[24,25] Even earlier initiation is appropriate in cases where symptoms are causing severe distress, or if there are safety concerns to self or others. A delay should be considered where symptoms are clearly related to substance use or a medical condition, and do not pose safety concerns.

The initial choice of antipsychotic should be made collaboratively with the patient and based on the side-effect and efficacy profile.[9,11–15] Dose scheduling, convenience, and the availability of a long-acting formulation of medication might also be factors to consider. If a patient is unable to engage in discussion, the input of friends and family should be sought, with the patient engaged in decision making as soon as it is clinically feasible. The use of digital tools allowing for medication side-effect comparison and risk of future metabolic syndrome might be useful to promote shared and informed decision making.[20–22] If no preference is expressed, an antipsychotic with a lower overall side-effect burden, such as a D2 partial agonist (eg, aripiprazole), is recommended.[7,20] Prolactin-raising antipsychotics should be avoided where possible, particularly in female patients of childbearing age. If medications with greater liability for metabolic adverse events, such as olanzapine or clozapine, are initiated, then the option to concomitantly initiate lifestyle modification and metformin should be offered to attenuate potential weight gain.[6,26–30] In cases of acutely agitated behaviour, short-term concomitant use of a benzodiazepine alongside a non-sedating, but less metabolically adverse, antipsychotic might be preferred over monotherapy with a more sedating, but metabolically adverse, antipsychotic.[31–34]

In the first episode of psychosis, antipsychotics should be started at a low dose.[13] Reassessment should occur soon (eg, 1 week) after starting medication, and the dose should be increased based on response and tolerability (example dosing schedules are shown in the table).[23] Monitoring of potential adverse effects is discussed below. In cases where there have been previous episodes of psychosis, a higher starting dose might be appropriate based on previous dosing and associated clinical response.

Although initial treatment will be with oral medication, the possibility of switching to a long-acting injectable preparation once tolerability is established should be discussed with patients early in treatment, considering the potential benefits (easier adherence, reduced relapse risk, and improved overall mortality) and drawbacks (difficulty in making rapid dose adjustments and need for injection).[35] The opportunity to use an long-acting injectable should be offered in a collaborative fashion, with care taken to avoid any perception of coercion by patients.

Treatment adherence

Adherence should be discussed from the outset and assessed regularly, particularly in cases of antipsychotic non-response or partial response.[13,36] An open and non-judgemental attitude should be used when discussing adherence, with attempts to address non-adherence undertaken using shared decision making. In addition to patient self-report, other methods should be used to assess adherence: plasma antipsychotic concentrations should be obtained if possible or, alternatively, pill counts or staff and carer reports can be used.[13,36–40] Low plasma antipsychotic concentrations frequently suggest non-adherence in the preceding days, but could also reflect rapid metaboliser status or poor absorption. If estimated adherence is less than 80% of the prescribed dose, then the option of an long-acting injectable formulation should be discussed.[41–43] Since non-adherence is often difficult to identify, it might be appropriate to discuss the use of a long-acting injectable even when there is no

	Initial daily dose (mg)	Dosing strategy	Target daily dose (mg)	Dosing strategy	Target daily dose (mg)	Dosing strategy	Maximum licensed dose (mg)*
Amisulpride†	100	Treat for 7 days and review; increase dose if response is tolerable and response inadequate	200	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	400	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	1200
Aripiprazole	5	Treat for 7 days and review; increase dose if response is tolerable and response inadequate; increase to 10 mg on day 4	15	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	20	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	30
Asenapine†	5	Treat for 7 days and review; increase dose if response is tolerable and response inadequate	10	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	20	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	20
Brexpiprazole	1	Treat for 7 days and review; increase dose if response is tolerable and response inadequate; increase to 2 mg on day 4	3	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	4	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	4
Cariprazine	1·5	Treat for 7 days and review; increase dose if response is tolerable and response inadequate	3	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	4·5	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	6
Lurasidone	37	Equivalent to 40 mg dose of lurasidone hydrochloride; treat for 7 days and review; increase dose is response if tolerable and response inadequate	74	Equivalent to 80 mg dose of lurasidone hydrochloride; treat for 14 days and review, increase dose is response if tolerable and response inadequate	111	Equivalent to 120 mg of lurasidone hydrochloride; treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	148
Paliperidone	3	Treat for 7 days and review; increase dose if response is tolerable and response inadequate	6	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	9	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	12
Olanzapine	5	Treat for 7 days and review; increase dose if response is tolerable and response inadequate	10	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	15	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	20
Quetiapine	50	Treat for 7 days and review, increase dose if response is tolerable and response inadequate; commence at 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4 (dosing split across 2 doses or once daily if using modified release)	400	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	600	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	750
Risperidone	1	Treat for 7 days and review; increase dose if response is tolerable and response inadequate	2	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	4	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	16
Ziprasidone†	40	Treat for 7 days and review; increase dose if response is tolerable and response inadequate	80	Treat for 14 days and review; increase dose if response is tolerable and response inadequate	160	Treat for 14 days and review; if ongoing positive symptoms, review adherence and, if adequate, consider antipsychotic switch	160

Lower doses might be required in the young, elderly, and those with comorbidities affecting pharmacokinetics (eg, renal disease). *Maximum licensed doses for some medications are substantially higher than doses used in usual clinical practice; these are provided for reference only and should not be seen as a target dose. †Dosing split across two doses.

Table: **Dosing strategies for first-episode psychosis using oral antipsychotic medication**

overt evidence of non-adherence, especially in cases of non-response or partial response. Shared decision making based on side-effect profiles should also be used when considering long-acting injectables.[9,11–15]

Dose reduction and discontinuation

To reduce the risk of side-effects, the lowest effective antipsychotic dose should always be used.[13] In some cases, the dose might need to be slowly tapered down, if it is causing adverse effects and symptoms are well controlled.[44] This dose reduction might be guided by antipsychotic blood concentrations, where available. If, following initial antipsychotic treatment, an individual has full remission of symptoms for over 2 years and has not previously had a relapse in the context of medication discontinuation, then the possibility of complete discontinuation should be

discussed, weighing the risks and potential benefits of treatment discontinuation (ie, the undesired effects of continuing medication versus the increased risk and adverse consequences of relapse).[10,45–49] In some circumstances, such as ongoing risk factors for relapse (eg, persistent substance use and poor premorbid adjustment)[50] or serious risk concerns, it might be appropriate to continue antipsychotic medication despite an extended period of remission. If a decision is made to discontinue medication, there should be robust individual and family psychoeducation around risks factors, and early signs of relapse. A gradual taper over at least 6 months should be used, with ongoing follow-up and careful monitoring of symptoms during withdrawal and following discontinuation, given the increased risk of relapse.[49]

Domain-specific management

Positive symptoms

Assuming good adherence, an individual's first antipsychotic medication should be given at a therapeutic dose for at least 4 weeks.[23] If significant positive symptoms persist, a switch to an alternative antipsychotic should be discussed. Shared decision making based on side-effect profiles should again be used, and an attempt should be made to switch to a compound with a different pharmacodynamic profile.[51,52] First-generation and second-generation antipsychotics are not a distinct category from either a pharmacological or clinical perspective and this classification should not be used to guide psychotropic choice.[53–55] For patients whose first-line treatment was a D2 partial agonist, a second-line treatment with amisulpride, risperidone, paliperidone, or olanzapine (with either samidorphan combination or concurrent metformin) might be considered.[56–62] Antipsychotic switching should involve gradual cross-titration informed by the half-life and receptor profile of each medication. Switching strategies are provided in the appendix (p 62) and the accompanying digital application.

If positive symptoms remain significant following a second treatment, for at least a 4-week treatment period at a therapeutic dose and with good adherence, then a reassessment of diagnosis, and any potential contributing factors (organic illness, substance use, etc) should be undertaken. In the case that a diagnosis of schizophrenia is confirmed, then a trial of clozapine should be considered.[63–68] Metformin should be offered concomitantly with clozapine to attenuate potential weight gain.[6,26–29] Clozapine dose should be titrated based on therapeutic response and tolerability, aiming for a dose sufficient to give a plasma level of at least 350 ng/mL, if therapeutic response is not reached at a lower plasma concentration.[69,70] If positive symptoms remain significant following a 12-week trial at a therapeutic plasma concentration, then the dose might be increased to produce a plasma concentration of up to 550 ng/mL.[69,70] Compared with a clozapine concentration of between 250 and 550 ng/mL, the number needed to treat to reach a response at clozapine concentrations above 550 ng/mL is 17.[71] Some people will only have a response only at higher clozapine concentrations. However, given the diminishing rates of response and increased risk of seizures at high clozapine concentrations, the decision to use clozapine concentrations above 550 ng/mL should be made in consultation with patients and carers, and prophylactic lamotrigine considered. If clozapine plasma concentrations are unavailable, the dose should be titrated based on tolerability and therapeutic response. Clozapine augmentation with amisulpride, aripiprazole, or electroconvulsive therapy might also be of benefit where significant positive symptoms remain.[69,70] Clozapine augmentation with an antidepressant can be considered in the case of ongoing negative symptoms.[69,70]

If a trial of clozapine is not possible or intolerable, olanzapine treatment can be considered.[64,65] There is no convincing trial evidence that high-dose antipsychotic treatment is superior to standard-dose treatment in treatment-resistant schizophrenia.[72–74] At all points, treatment decisions should consider psychological interventions such as cognitive behavioural therapy as an additional means of managing positive symptoms.

Negative symptoms

In the case of persistent negative symptoms, secondary causes should be considered and addressed. These include persistent positive symptoms, depressive symptoms, substance misuse, social isolation, medical illness (eg, hypothyroidism), and the side-effects of antipsychotic medication (eg, extrapyramidal symptoms, sedation, and marked weight gain leading to sleep apnoea). Psychosocial interventions should be offered, both to address psychological factors that might exacerbate or maintain negative symptoms and to encourage social engagement.[75–79]

If positive symptoms are well controlled, then a gradual reduction of antipsychotic dose, while remaining within the therapeutic range, might be considered.[49,80] If a switch in antipsychotic medication is considered, then cariprazine or aripiprazole are suitable options.[7,81,82] Low-dose amisulpride (eg, 50 mg twice daily) could also be considered in cases of predominant negative symptoms where positive symptoms are not a concern.[81]

Antidepressant augmentation in the absence of a diagnosis of depression might still have a beneficial effect on negative symptoms and could be offered, although any benefit might be modest and potential pharmacokinetic and pharmacodynamic (eg, serotonin syndrome) interactions should be considered.[83] As with antipsychotic medication, shared decision making informed by side-effect profiles should be used.

If risks and benefits are clearly explained, a trial of aripiprazole augmentation in individuals not already prescribed a D2 partial agonist could be offered.[84]

Depressive symptoms

Both psychological therapy for depression and antidepressant medication should be considered.[7,85,86] No specific antidepressant has been shown to have superiority over any other for the treatment of depression in schizophrenia.[83] As with antipsychotic medication, shared decision making informed by side-effect profiles should be used.

If a switch in antipsychotic is considered, then a D2 partial agonist or amisulpride are suitable options.[7] The potential contribution of negative symptoms should also be considered, and the strategies discussed above (eg, cautious antipsychotic dose reduction) should be used if appropriate.

Cognitive symptoms

The anticholinergic burden of a patient's medication regimen should be reviewed, and attempts should be made to minimise this burden.[87] Of the antipsychotic medications, clozapine, olanzapine, and quetiapine have the highest central anticholinergic activity. If positive symptoms are well controlled, then a gradual reduction of antipsychotic dose while remaining within the therapeutic range might be considered.[87–89] Cognitive remediation therapy should also be considered where available.

Monitoring antipsychotic treatment

Before starting antipsychotic treatment, the following measures should be obtained: BMI, waist circumference, blood pressure, HbA_{1c}, glucose, lipids, prolactin, liver function tests, urea and electrolytes, full blood count, and electrocardiogram.[26] Fasting glucose should be re-checked 4 weeks following initiation. Pragmatically, if a fasting sample cannot be obtained, a random sample can be obtained as an initial screening measure; then, is this is not in the healthy range, a fasting measure should be prioritised. BMI, waist circumference, and blood pressure should be checked weekly for 6 weeks. A similar schedule should be used following a switch of antipsychotic. All these measures should then be repeated and reviewed after 3 months of antipsychotic treatment and annually thereafter. In the case of clozapine treatment, it is desirable to follow the specific recommendations of available guidelines before and during initiation of the drug.[69]

Adverse effects and cardiometabolic health

Antipsychotic medications are associated with a wide range of side-effects, and these might contribute to non-adherence and pose significant physical health comorbidities. Prompt and effective management is crucial to improving both physical and mental health outcomes. Psychiatric care providers should play a central role in monitoring and managing these adverse effects.

Cardiometabolic side-effects

Lifestyle advice (healthy diet, promotion of physical activity, and tobacco cessation) should be offered to all patients,[27,28,90] and adjunctive metformin might be offered when starting antipsychotics with a poor cardiometabolic profile (olanzapine and clozapine).[27,29] Before commencing metformin, renal function should be assessed and metformin should be avoided in those with renal failure.[30] The target dose and initiation regimen of metformin is the same as that used for the treatment of diabetes (eg, in the UK); treatment should commence at 500 mg once daily and then increased in 500 mg increments every 2 weeks up to 1 g twice daily, dependent on tolerability. If available, a modified release preparation should be used to minimise risk of gastrointestinal side-effects. Ongoing monitoring should include annual liver function, HbA_{1c}, renal function, and vitamin B12.[91]

Interventions should be considered in the context of rapid weight gain (defined as ≥5% occurring within 3 months of starting any antipsychotic); BMI over 30 kg/m² (or ≥27·5 kg/m² for those of South Asian, Chinese, other Asian, Middle Eastern, Hispanic, Black African, or African-Caribbean family backgrounds); or BMI over 27 kg/m² (or ≥24·5 kg/m² for the family backgrounds described previously) and the presence of 1 or more components of the metabolic syndrome.[26] Available treatment strategies can include a switch to an antipsychotic with a more benign metabolic profile,[92] adjunctive metformin treatment,[93] or adjunctive treatment with a GLP-1 receptor agonist.[94]

In the case of raised cholesterol concentrations, a statin should be offered.[26,30] Metformin should be offered for HbA_{1c} concentrations between 5·7% and 6·5%, and a fasting glucose of between 5·5 mmol/L and 7 mmol/L. In the case of HbA_{1c}, concentration of 6·5% or more, random glucose 11 mmol/L or more, or fasting glucose of 7 mmol/L or more, a diabetes specialist review should be arranged.[26,30] In the case of raised blood pressure, an antihypertensive should be offered.[26,30] These interventions can be undertaken in conjunction with primary care services.

Dopamine D2 receptor occupancy-mediated side-effects

In individuals who show signs of tardive dyskinesia, a switch to clozapine, olanzapine, quetiapine, or a D2 partial agonist should be discussed.[95] Following a switch, or if a switch is not possible, then the use of an adjunctive vesicular monoamine transporter 2 inhibitor might be considered if symptoms remain significant.[96]

In patients experiencing parkinsonism related to D2 blockade, dose reduction should be considered or a switch to a D2 partial agonist or antagonist with a weaker affinity for the D2 receptor.[13] Adjunctive treatment with an anticholinergic agent is not usually recommended, although, where alternative strategies are not appropriate, this anticholinergic agent might be a reasonable treatment option.[13,96,97]

Akathisia can potentially be managed with dose reduction.[98] A switch to quetiapine or olanzapine can also be considered.[98] Alternatively, adjunctive propranolol

(10 mg or up to 30 mg, two to three times daily) or mirtazapine (15 mg once daily) might be of some benefit.[99,100]

In the case of symptomatic hyperprolactinaemia (eg, galactorrhoea and sexual side-effects), the possibility of switching to a dopamine partial agonist should be discussed.[101,102] Alternatively, adjunctive low-dose aripiprazole (5 mg once daily) can be considered.[101,102]

Patients should be counselled on the risks of untreated asymptomatic hyperprolactinaemia, including reduced bone mineral density and, for women, a clinically significant increased risk of breast cancer.[103–105] Where appropriate to take action, or in the case of symptomatic hyperprolactinaemia, the possibility of switching to a D2 partial agonist should be discussed.[101,102] Alternatively, adjunctive low-dose aripiprazole can be considered.[101,102]

Substance use comorbidities

Substance use comorbidities are common in individuals with schizophrenia. Information, education, and a non-judgmental supportive approach should be used. Co-working with specialist substance use disorder services should be encouraged. Varenicline, bupropion, and nicotine replacement therapy have been shown to be as effective in reducing smoking in people with schizophrenia.[106] Patients should be counselled on reducing tobacco use and offered pharmacological interventions where appropriate.[26] Naltrexone has shown efficacy for reducing harmful use of alcohol in individuals with schizophrenia and should be offered where appropriate.[107]

Considerations

Digital application

For more on this **application** see www.psymatik.com/guidelines/scz

Following the development of the treatment algorithm, we designed a web application using the Django framework. The application is accessible via both desktop and mobile devices. Users input current symptoms, medications, and side-effects and are presented with the relevant contents of the guidelines.

Limitations

Development of the INTEGRATE guidelines, although evidence informed, used a consensus-based approach. In some areas, particularly the management of negative symptoms, long-term maintenance strategies, and clozapine-resistant psychosis, there is currently little evidence. As a result, not all recommendations in the guideline are based on high-level evidence, and consensus often had to bridge gaps where there is little evidence. The absence of high-level evidence also has the effect that there are some potential inconsistencies with previously published guidelines; for example, the current guidance to consider a switch in antipsychotic after 4 weeks of inadequate response is not in alignment with previous guidance for the diagnosis of treatment resistance.[63] In addition, as this guideline focused on pharmacological management of schizophrenia, it does not attempt to comment on the specifics of psychosocial and psychological interventions.

The results of epidemiological studies in 2019 and 2023 have raised the possibility that antipsychotic polypharmacy might be associated with some benefits.[108,109] The current guidelines do not discuss polypharmacy other than in the case of aripiprazole augmentation, or the augmentation of clozapine.

GLP-1 receptor agonists are safe and effective treatments for individuals living with obesity who have not responded to other treatments.[110] We propose this indication in the current guidelines. There is evidence that these treatments are not associated with adverse psychiatric effects, and there is no evidence that people with psychotic disorders would benefit less from these treatments than the general population.[94,111–113] Although there is some evidence directly in individuals with schizophrenia, more work is needed within this population.[94] Future guidelines might be able to comment more broadly on these areas as further evidence arises.

The guideline attempts to provide global recommendations, but differences in health-care resources, accessibility, and medication availability across countries might affect the applicability of some recommendations in low-resource settings. This guideline focuses on adults with schizophrenia. Treatment approaches for children and adolescents, who might have specific needs and responses to pharmacotherapy, are not covered in depth and will require separate guidance.

Future directions

All currently efficacious drugs for the treatment of the positive symptoms of schizophrenia show some occupancy of the dopamine D2 receptor with either antagonist or partial agonist activity, and the use of these compounds to treat psychotic symptoms is a central component of the current guideline. It is hoped and highly probable that, in the future, additional pharmacological, digital, and non-pharmacological treatments, including treatments with new mechanisms of action and efficacy beyond positive symptoms, will become available as suitable treatment options. Xanomeline and trospium in combination has recently been approved for the treatment of schizophrenia and there are other promising treatments in phase 3 trials that act via non-postsynaptic dopamine antagonism mechanisms.[114,115] If these compounds are approved for clinical use, a prompt appraisal of their position in treatment will be required. Similarly, advances in the prediction of treatment response and prognostication might mean that, in due course, integrating predictive tools might be appropriate.[116,117] The optimal approach to tapering antipsychotic medication when reducing dose

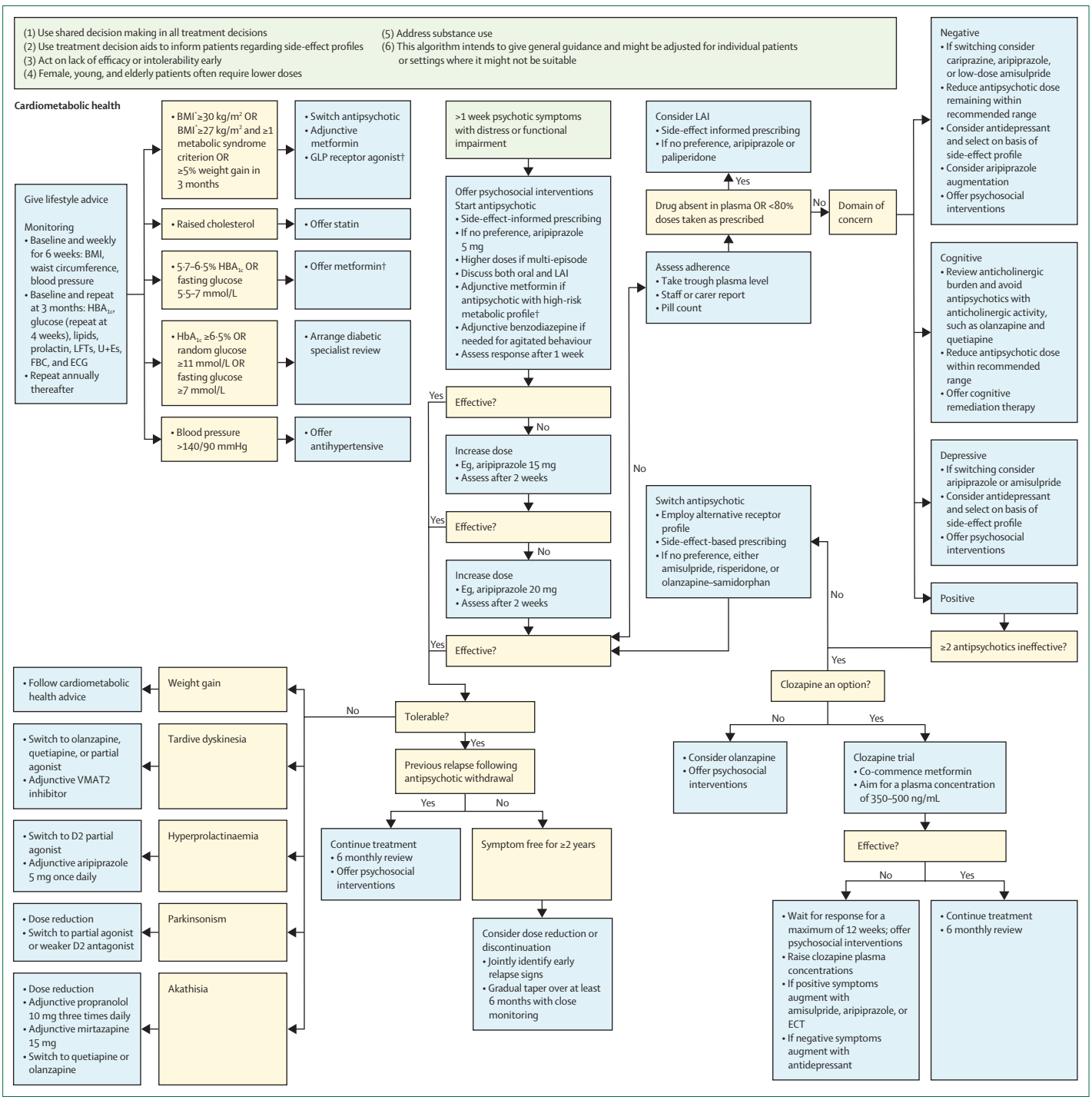

Figure: **Algorithmic summary of treatment guidelines for schizophrenia**

HBA_{1c}=haemoglobin A_{1c}. LFT=liver function test. U+E=urea and electrolyte. FBC=full blood count. ECG=electrocardiogram. VMAT2=vesicular monoamine transporter 2. LAI=long-acting injectable. ECT=electroconvulsive therapy. *Lower BMI thresholds by 2·5 kg/m² for people from South Asian, Chinese, other Asian, Middle Eastern, Hispanic, Black African, or African-Caribbean family backgrounds. †When using metformin start at 500 mg once per day, aim for minimum of 1 g once per day and maximum of 1 g twice per day. Check B12 concentrations annually.

or discontinuing is an active area of research, and we aim to include more precise guidance in the future.[44,118] Finally, rapidly evolving treatments for overweight and obesity promise to revolutionise the metabolic health of people with schizophrenia. Future work will also aim to examine the implementation of the guidelines, including the effect on clinical outcomes. Ongoing work using regularly updated living umbrella reviews will facilitate

Search strategy and selection criteria

A search was performed using (schizophrenia OR psychosis) AND (systematic review OR meta analysis) AND (random OR RCT OR trial OR clozapine OR LAI OR depot OR long acting injectable). PubMed and PsycINFO databases were searched from inception until July 21, 2023. For each population, intervention, comparison, and outcome combination, we selected the largest relevant meta-analysis, and presented the relevant data from this in the survey question. 2061 papers were retrieved, of which 721 were potentially eligible to inform the review; 83 were eventually used to develop the questionnaire.

prompt updating of these guidelines, with updates planned at 5-yearly intervals.

Conclusion

The treatment of individuals with schizophrenia is a central component of general psychiatric practice. Effective treatments exist, but maximising therapeutic effects requires a dynamic and flexible approach involving patients in decision making. The current INTEGRATE guidelines collate an extensive literature on the pharmacological treatment of schizophrenia; the key recommendations are summarised in the figure. These include a focus on metabolic health from treatment initiation, timely assessment and management of non-response, symptom domain-specific interventions, mitigation of side effects, and the prompt use of clozapine in cases of treatment resistance.

The INTEGRATE Advisory Group

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Contributors

RAM, TP, SH, and DS conceived the idea. IV, RAM, TP, SH, MS, and DS designed and undertook the umbrella review. RAM and TP designed the digital application. RAM, TP, IV, SH, OOA, NAC, CUC, MH, ODH, JMK, TK, AK-G, BL, CHLM, SR, MS, IES, HT, HU, GV, NW, and DS designed the survey questionnaires. TP, RAM, TK, DS, MH, and EC ran the SIRS workshop. All authors, including the INTEGRATE advisory group, completed the surveys. RAM, TP, IV, SH, and DS drafted the initial manuscript. All authors including the INTEGRATE advisory group completed the surveys, reviewed and amended the initial draft, and approved the final manuscript.

Declaration of interests

RAM has received speaker or consultancy fees, or both, from Boehringer Ingelheim, Janssen, Karuna, Lundbeck, Newron, Otsuka, and Viatris, and co-directs a company that designs digital resources to support treatment of mental ill health. TP has contributed to educational and advisory meetings organised by Recordati, Lundbeck, Otsuka, Janssen, CNX Therapeutics, Sunovion, ROVI Biotech, Schwabe Pharma, and Lecturing Minds Stockholm. He receives book royalties from Wiley Blackwell. He co-directs a company that designs digital resources to support treatment of mental ill health. CUC has been a consultant and advisor to or has received honoraria from AbbVie, Alkermes, Allergan, Angelini, Aristo, Boehringer Ingelheim, Bristol Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Eli Lilly, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Johnson & Johnson Innovative Medicine (formerly Janssen), Karuna, LB Pharma, Lundbeck, MedInCell, MedLink, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Saladax, Sanofi, Seqirus, Servier, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris, and Xenon Pharmaceuticals. He provided expert testimony for Janssen, Lundbeck, and Otsuka. He served on a Data safety monitoring board for Compass Pathways, IntraCellular Therapies, Relmada, Reviva, and Rovi. He has received grant support from Boehringer-Ingelheim, Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, Terran. MH has received consultant and speaker fees from Alkermes and consultant fees from Merck. ODH has received investigator-initiated research funding from or participated in advisory or speaker meetings organised by AbbVie, Alkermes, Angellini, Autifony, Biogen, Boehringer Ingelheim, Delix, Eli Lilly, Elysium, Heptares, Global Medical Education, Invicro, Janssen, Karuna, Lundbeck, Merck, Neumora, Neurocrine, Ontrack and Pangea, Otsuka, Sunovion, Teva, Recordati, Roche, Rovi, and Mylan (a subsidiary of Viatris); was previously a part-time employee of Lundbeck. JMK has received a research grant and manages the funds from Lundbeck, Otsuka, Janssen, and Sunovion; receives ownership interest from Vanguard Research Group (private), LB Pharmaceuticals (private), North Shore Therapeutics (private), HealthRhythms (private), Cerevel (public), and Karuna (public); and receives consulting fees from Click Therapeutics, Karuna, Lundbeck, Merck, Newron, Novartis, Otsuka, Sumitomo, Alkermes, Allergan, Boehringer Ingelheim, Cerevel, Dainippon Sumitomo, Lundbeck, HealthRhythms, HLS Therapeutics, Indivior, Intracellular Therapies, Janssen Pharmaceutical, Johnson and Johnson, Karuna Therapeutics, LB Pharmaceuticals, Merck, Minerva, Neurocrine, NW PharmaTech, Otsuka, Roche, Saladax, Sunovion, and Teva. BL has received funding from Johnson and Johnson, ArgenX, Takeda, and Arialys for scientific advice. MS has received honoraria and has been a consultant for Angelini, AbbVie, Boehringer Ingelheim, Lundbeck, and Otsuka. HT has participated in research projects funded by grants from Janssen to their employing institution; and has received personal fees from Gedeon Richter, Janssen, Lundbeck, and Otsuka. HU has received grants from Daiichi Sankyo, Eisai, Mochida, Otsuka, and Sumitomo Pharma, has received speaker fees from Eisai, Lundbeck, Meiji Seika Pharma, Otsuka, Boehringer Ingelheim Japan, Merck Sharp & Dohme, and Sumitomo Pharma, and has received advisory board fees from Lundbeck, Sumitomo Pharma, Takeda Pharmaceutical Company, and Boehringer Ingelheim Japan for the past 3 years. SLR has received honoraria for advising and consulting from Boehringer Ingelheim. All other authors declare no competing interests.

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