INTEGRATE: international guidelines for the algorithmic treatment of schizophrenia

Robert A McCutcheon*, Toby Pillinger*, Ioana Varvari, Sean Halstead, Olatunde O Ayinde, Nicolás A Crossley, Christoph U Correll, Margaret Hahn, Oliver D Howes, John M Kane, Thomas Kabir, Åsa Konradsson-Geuken, Belinda Lennox, Christy Lai Ming Hui, Susan L Rossell, Marco Solmi, Iris E Sommer, Heidi Taipale, Hiroyuki Uchida, Ganesan Venkatasubramanian, Nicola Warren, The INTEGRATE Advisory Group, Dan Siskind

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.

*Contributed equally

Department of Psychiatry, University of Oxford, Oxford, UK (R A McCutcheon PhD, I Varvari MRCPsych, T Kabir PhD, Prof B Lennox DM); **Oxford Health NHS Foundation Trust, Oxford, UK** (R A McCutcheon, I Varvari, Prof B Lennox); **Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK** (R A McCutcheon, T Pillinger PhD, Prof O D Howes DM); **South London and Maudsley NHS Foundation Trust, London, UK** (T Pillinger); **Medical School, The University of Queensland, Brisbane, QLD, Australia** (S Halstead MD, N Warren PhD, Prof D Siskind PhD); **Addiction and Mental Health Service, Metro South Health, Brisbane, QLD, Australia** (S Halstead, N Warren, Prof D Siskind); **Department of Psychiatry, College of Medicine, University of Ibadan, Ibadan, Nigeria** (O O Ayinde MS); **Department of Psychiatry, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile** (N A Crossley PhD); **Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA** (Prof C U Correll MD, Prof J M Kane MD); **Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempsted, NY, USA** (Prof C U Correll, Prof J M Kane); **The Feinstein Institute for Medical Research, Northwell Health, New Hyde Park, NY, USA** (Prof C U Correll, Prof J M Kane); **Charité – Universitätsmedizin Berlin, Berlin, Germany**

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

(Prof C U Correll); **Centre for Addiction and Mental Health, Toronto, ON, Canada** (Prof M Hahn PhD); **Department of Pharmacology & Toxicology, University of Toronto, Toronto, ON, Canada** (Prof M Hahn); **Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada** (Prof M Hahn); **Department of Psychiatry, University of Toronto, Toronto, ON, Canada** (Prof M Hahn); **Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark** (Prof M Hahn); **Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden** (Å Konradsson-Geuken PhD); **Swedish Schizophrenia Association, Stockholm, Sweden** (Å Konradsson-Geuken); **Department of Psychiatry, University of Hong Kong, Hong Kong Special Administrative Region, China** (C L M Hui PhD); **Centre for Mental Health, Swinburne University of Technology, Melbourne, VIC, Australia** (Prof S L Rossell PhD); **SCIENCES Lab, University of Ottawa, Ottawa, ON, Canada** (M Solmi PhD); **Champlain First Episode Psychosis Program, The Ottawa Hospital, Ottawa, ON, Canada** (M Solmi); **Ottawa Hospital Research Institute, Ottawa, ON, Canada** (M Solmi); **Department of Child and Adolescent Psychiatry, Charité – Universitätsmedizin Berlin, Berlin, Germany** (M Solmi); **University Medical Center Groningen, Groningen, Netherlands** (Prof I E Sommer MD PhD); **Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden** (H Taipale PhD); **Niuvanniemi Hospital, Kuopio, Finland** (H Taipale); **Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan** (Prof H Uchida MD PhD); **Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, India** (Prof G Venkatasubramanian MD PhD)

	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

Correspondence to:
Robert A McCutcheon,
Department of Psychiatry,
University of Oxford,
Oxford OX3 7JX, UK
robert.mccutcheon@psych.
ox.ac.uk

See Online for appendix

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

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

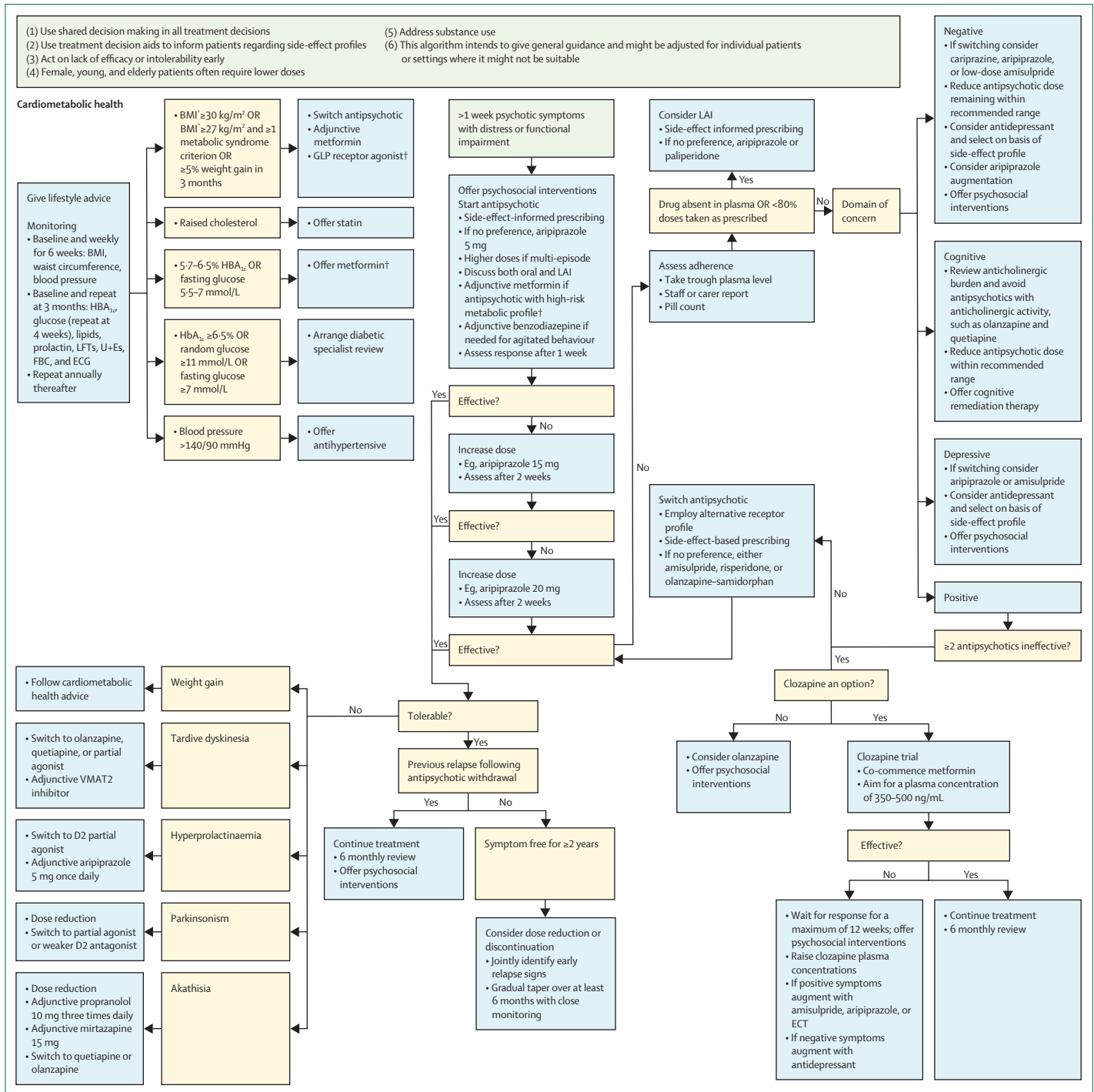For more on this **application** see www.psymatik.com/guidelines/scz

(1) Use shared decision making in all treatment decisions
(2) Use treatment decision aids to inform patients regarding side-effect profiles
(3) Act on lack of efficacy or intolerability early
(4) Female, young, and elderly patients often require lower doses
(5) Address substance use
(6) This algorithm intends to give general guidance and might be adjusted for individual patients or settings where it might not be suitable

Cardiometabolic health

Give lifestyle advice

Monitoring
- Baseline and weekly for 6 weeks: BMI, waist circumference, blood pressure
- Baseline and repeat at 3 months: HBA$_{1c}$, glucose (repeat at 4 weeks), lipids, prolactin, LFTs, U+Es, FBC, and ECG
- Repeat annually thereafter

- BMI*≥30 kg/m² OR BMI*≥27 kg/m² and ≥1 metabolic syndrome criterion OR ≥5% weight gain in 3 months
  → • Switch antipsychotic • Adjunctive metformin • GLP receptor agonist†

- Raised cholesterol → • Offer statin

- 5·7–6·5% HBA$_{1c}$ OR fasting glucose 5·5–7 mmol/L → • Offer metformin†

- HbA$_{1c}$ ≥6·5% OR random glucose ≥11 mmol/L OR fasting glucose ≥7 mmol/L → • Arrange diabetic specialist review

- Blood pressure >140/90 mmHg → • Offer antihypertensive

>1 week psychotic symptoms with distress or functional impairment
↓
Offer psychosocial interventions
Start antipsychotic
- Side-effect-informed prescribing
- If no preference, aripiprazole 5 mg
- Higher doses if multi-episode
- Discuss both oral and LAI
- Adjunctive metformin if antipsychotic with high-risk metabolic profile†
- Adjunctive benzodiazepine if needed for agitated behaviour
- Assess response after 1 week
↓
Effective? — Yes →
↓ No
Increase dose
- Eg, aripiprazole 15 mg
- Assess after 2 weeks
↓
Effective? — Yes →
↓ No
Increase dose
- Eg, aripiprazole 20 mg
- Assess after 2 weeks
↓
Effective? — Yes →
↓
Tolerable? — No →
↓ Yes
Previous relapse following antipsychotic withdrawal
— Yes → Continue treatment • 6 monthly review • Offer psychosocial interventions
— No → Symptom free for ≥2 years
↓
Consider dose reduction or discontinuation
- Jointly identify early relapse signs
- Gradual taper over at least 6 months with close monitoring

Consider LAI
- Side-effect informed prescribing
- If no preference, aripiprazole or paliperidone
↓ Yes
Drug absent in plasma OR <80% doses taken as prescribed — No → Domain of concern
↑
Assess adherence
- Take trough plasma level
- Staff or carer report
- Pill count

Switch antipsychotic
- Employ alternative receptor profile
- Side-effect-based prescribing
- If no preference, either amisulpride, risperidone, or olanzapine–samidorphan

Domain of concern:

Negative
- If switching consider cariprazine, aripiprazole, or low-dose amisulpride
- Reduce antipsychotic dose remaining within recommended range
- Consider antidepressant and select on basis of side-effect profile
- Consider aripiprazole augmentation
- Offer psychosocial interventions

Cognitive
- Review anticholinergic burden and avoid antipsychotics with anticholinergic activity, such as olanzapine and quetiapine
- Reduce antipsychotic dose within recommended range
- Offer cognitive remediation therapy

Depressive
- If switching consider aripiprazole or amisulpride
- Consider antidepressant and select on basis of side-effect profile
- Offer psychosocial interventions

Positive
↓
≥2 antipsychotics ineffective?
↓ Yes
Clozapine an option?
— No → • Consider olanzapine • Offer psychosocial interventions
— Yes → Clozapine trial
- Co-commence metformin
- Aim for a plasma concentration of 350–500 ng/mL
↓
Effective?
— No →
- Wait for response for a maximum of 12 weeks; offer psychosocial interventions
- Raise clozapine plasma concentrations
- If positive symptoms augment with amisulpride, aripiprazole, or ECT
- If negative symptoms augment with antidepressant
— Yes →
- Continue treatment
- 6 monthly review

Side-effects:

- Weight gain → • Follow cardiometabolic health advice
- Tardive dyskinesia → • Switch to olanzapine, quetiapine, or partial agonist • Adjunctive VMAT2 inhibitor
- Hyperprolactinaemia → • Switch to D2 partial agonist • Adjunctive aripiprazole 5 mg once daily
- Parkinsonism → • Dose reduction • Switch to partial agonist or weaker D2 antagonist
- Akathisia → • Dose reduction • Adjunctive propranolol 10 mg three times daily • Adjunctive mirtazapine 15 mg • Switch to quetiapine or olanzapine

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
Ofer Agid, Celso Arango, Andrea de Bartolomeis, Robert A Bittner, Rodrigo A Bressan, Robert W Buchanan, Giacomo Cecere, Eric Y H Chen, Leslie Citrome, Sonia Dollfus, Serdar M Dursun, Bjørn H Ebdrup, Helio Elkis, Robin Emsley, Emilio Fernandez-Egea, Wolfgang Fleischhacker, Oliver Freudenreich, Ary Gadelha, Shiral S Gangadin, Fiona Gaughran, Jaime Eduardo Cecilio Hallak, Alkomiet Hasan, Philipp Homan, Sameer Jauhar, Stefan Kaiser, Jun Soo Kwon, Jimmy Lee, Stefan Leucht, Jan Libiger, Markus F Leweke, James H MacCabe, Stephen R Marder, Tiago Reis Marques, Ingrid Melle, Armida Mucci, Shinichiro Nakajima, Brian O'Donoghue, Akin Ojagbemi, Benjamin I Perry, J L Roos, Jose M Rubio, Janusz K Rybakowski, Gabriele Sachs, Cynthia O Siu, Takefumi Suzuki, David M Taylor, Hiroyoshi Takeuchi, Jagadisha Thirthalli, Neil Thomas, Alp Üçok, Shivarama Varambally, Octavian Vasiliu, Elias Wagner.

References

1 McCutcheon RA, Marques TR, Howes OD. Schizophrenia—an overview. *JAMA Psychiatry* 2020; **77**: 201–10.

2 Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005; **2**: e141.

3 Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. *Lancet* 2022; **399**: 473–86.

4 Solmi M, Seitidis G, Mavridis D, et al. Incidence, prevalence, and global burden of schizophrenia - data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Mol Psychiatry* 2023; **28**: 5319–27.

5 Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry* 2012; **201**: 481–85.

6 Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry* 2020; **7**: 64–77.

7 Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; **394**: 939–51.

8 NICE. Psychosis and schizophrenia in adults: prevention and management. NICE Clinical Guidelines, No 178. National Institute for Health and Care Excellence, 2014.

9 Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry* 2020; **177**: 868–72.

10 Correll CU, Martin A, Patel C, et al. Systematic literature review of schizophrenia clinical practice guidelines on acute and maintenance management with antipsychotics. *Schizophrenia* 2022; **8**: 5.

11 NICE. Shared decision making. 2021. https://www.nice.org.uk/guidance/ng197 (accessed July 23, 2024).

12 Hamann J, Leucht S, Kissling W. Shared decision making in psychiatry. *Acta Psychiatr Scand* 2003; **107**: 403–09.

13 Taylor DM, Barnes TRE, Young AH. The Maudsley prescribing guidelines in psychiatry, 14th edn. Wiley-Blackwell, 2021.

14 Galletly C, Castle D, Dark F, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Aust N Z J Psychiatry* 2016; **50**: 410–72.

15 Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia - a short version for primary care. *Int J Psychiatry Clin Pract* 2017; **21**: 82–90.

16 Brand BA, Haveman YRA, de Beer F, de Boer JN, Dazzan P, Sommer IEC. Antipsychotic medication for women with schizophrenia spectrum disorders. *Psychol Med* 2022; **52**: 649–63.

17 Uchida H, Mamo DC, Mulsant BH, Pollock BG, Kapur S. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. *J Clin Psychiatry* 2009; **70**: 397–405.

18 Rajkumar AP, Poonkuzhali B, Kuruvilla A, Jacob M, Jacob KS. Clinical predictors of serum clozapine levels in patients with treatment-resistant schizophrenia. *Int Clin Psychopharmacol* 2013; **28**: 50–56.

19 Hägg S, Spigset O, Mjörndal T, Dahlqvist R. Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 2000; **49**: 59–63.

20 Pillinger T, Howes OD, Correll CU, et al. Antidepressant and antipsychotic side-effects and personalised prescribing: a systematic review and digital tool development. *Lancet Psychiatry* 2023; **10**: 860–76.

21 Leucht S, Siafis S, Rodolico A, et al. Shared Decision Making Assistant (SDMA) and other digital tools for choosing antipsychotics in schizophrenia treatment. *Eur Arch Psychiatry Clin Neurosci* 2023; **273**: 1629–31.

22 Perry BI, Osimo EF, Upthegrove R, et al. Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): a cardiometabolic risk prediction algorithm for young people with psychosis. *Lancet Psychiatry* 2021; **8**: 589–98.

23 Samara MT, Leucht C, Leeflang MM, et al. Early improvement as a predictor of later response to antipsychotics in schizophrenia: a diagnostic test review. *Am J Psychiatry* 2015; **172**: 617–29.

24 Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust N Z J Psychiatry* 2005; **39**: 964–71.

25 NICE. Psychosis and schizophrenia in children and young people: recognition and management. NICE Clinical Guidelines, No 155. National Institute for Health and Care Exceellence, 2016.

26 Perry BI, Mitchell C, Holt RI, Shiers D, Chew-Graham CA. Lester positive cardiometabolic resource update: improving cardiometabolic outcomes in people with severe mental illness. *Br J Gen Pract* 2023; **73**: 488–89.

27 Vancampfort D, Firth J, Correll CU, et al. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry* 2019; **18**: 53–66.

28 Holt RIG, Gossage-Worrall R, Hind D, et al. Structured lifestyle education for people with schizophrenia, schizoaffective disorder and first-episode psychosis (STEPWISE): randomised controlled trial. *Br J Psychiatry* 2019; **214**: 63–73.

29 Wang Y, Wang D, Cheng J, et al. Efficacy and tolerability of pharmacological interventions on metabolic disturbance induced by atypical antipsychotics in adults: a systematic review and network meta-analysis. *J Psychopharmacol* 2021; **35**: 1111–19.

30 Firth J, Siddiqi N, Koyanagi A, et al. The *Lancet Psychiatry* Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry* 2019; **6**: 675–712.

31 Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 1997; **15**: 335–40.

32 Barbee JG, Mancuso DM, Freed CR, Todorov AA. Alprazolam as a neuroleptic adjunct in the emergency treatment of schizophrenia. *Am J Psychiatry* 1992; **149**: 506–10.

33 Garza-Treviño ES, Hollister LE, Overall JE, Alexander WF. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation. *Am J Psychiatry* 1989; **146**: 1598–601.

34 Zaman H, Sampson SJ, Beck AL, et al. Benzodiazepines for psychosis-induced aggression or agitation. *Cochrane Database Syst Rev* 2017; **12**: CD003079.

35 Arango C, Fagiolini A, Gorwood P, et al. Delphi panel to obtain clinical consensus about using long-acting injectable antipsychotics to treat first-episode and early-phase schizophrenia: treatment goals and approaches to functional recovery. *BMC Psychiatry* 2023; **23**: 453.

36 McCutcheon R, Beck K, D'Ambrosio E, et al. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. *Acta Psychiatr Scand* 2018; **137**: 39–46.

37 El Alili M, Vrijens B, Demonceau J, Evers SM, Hiligsmann M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *Br J Clin Pharmacol* 2016; **82**: 268–79.

38 Velligan DI, Wang M, Diamond P, et al. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. *Psychiatr Serv* 2007; **58**: 1187–92.

39 Larsen KG, Areberg J, Åström DO. Are self-reported and self-monitored adherence good proxies for reaching relevant plasma concentrations?: Experiences from a study of anti-depressants in healthy volunteers. *Clin Trials* 2021; **18**: 505–10.

40 Kristiansen O, Sverre E, Peersen K, et al. The relationship between directly measured statin adherence, self-reported adherence measures and cholesterol levels in patients with coronary heart disease. *Atherosclerosis* 2021; **336**: 23–29.

41 Ascher-Svanum H, Zhu B, Faries DE, Lacro JP, Dolder CR, Peng X. Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. *Patient Prefer Adherence* 2008; **2**: 67–77.

42 Cahaya N, Kristina SA, Widayanti AW, Green J. Interventions to improve medication adherence in people with schizophrenia: a systematic review. *Patient Prefer Adherence* 2022; **16**: 2431–49.

43 Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 2009; **70** (suppl 4): 1–46, quiz 47–48.

44　McCutcheon RA, Taylor D, Rubio J, et al. Does slow and steady win the race? Rates of antipsychotic discontinuation, antipsychotic dose, and risk of psychotic relapse. *Schizophr Bull* 2024; **50:** 513–20.

45　Ostuzzi G, Vita G, Bertolini F, et al. Continuing, reducing, switching, or stopping antipsychotics in individuals with schizophrenia-spectrum disorders who are clinically stable: a systematic review and network meta-analysis. *Lancet Psychiatry* 2022; **9:** 614–24.

46　Højlund M, Kemp AF, Haddad PM, Neill JC, Correll CU. Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic review and meta-analysis of randomised controlled trials. *Lancet Psychiatry* 2021; **8:** 471–86.

47　Bogers JPAM, Hambarian G, Walburgh Schmidt N, Vermeulen JM, de Haan L. Risk factors for psychotic relapse after dose reduction or discontinuation of antipsychotics in patients with chronic schizophrenia. A meta-analysis of randomized controlled trials. *Schizophr Bull* 2023; **49:** 11–23.

48　Tani H, Takasu S, Uchida H, Suzuki T, Mimura M, Takeuchi H. Factors associated with successful antipsychotic dose reduction in schizophrenia: a systematic review of prospective clinical trials and meta-analysis of randomized controlled trials. *Neuropsychopharmacology* 2020; **45:** 887–901.

49　Kishi T, Ikuta T, Matsui Y, et al. Effect of discontinuation v. maintenance of antipsychotic medication on relapse rates in patients with remitted/stable first-episode psychosis: a meta-analysis. *Psychol Med* 2019; **49:** 772–79.

50　Alvarez-Jimenez M, Priede A, Hetrick SE, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. *Schizophr Res* 2012; **139:** 116–28.

51　McCutcheon RA, Harrison PJ, Howes OD, McGuire PK, Taylor D, Pillinger T. Data driven taxonomy for antipsychotic medication: a new classification system. *Biol Psychiatry* 2023; **94:** 561–68.

52　Zohar J, Stahl S, Moller H-J, et al. A review of the current nomenclature for psychotropic agents and an introduction to the neuroscience-based nomenclature. *Eur Neuropsychopharmacol* 2015; **25:** 2318–25.

53　McCutcheon RA, Cannon A, Parmer S, Howes OD. How to classify antipsychotics: time to ditch dichotomies? *Br J Psychiatry* 2024; **224:** 20–25.

54　Zohar J, Nutt DJ, Kupfer DJ, et al. A proposal for an updated neuropsychopharmacological nomenclature. *Eur Neuropsychopharmacol* 2014; **24:** 1005–14.

55　McCutcheon RA, Harrison PJ, Howes OD, McGuire PK, Taylor DM, Pillinger T. Data-driven taxonomy for antipsychotic medication: a new classification system. *Biol Psychiatry* 2023; **94:** 561–68.

56　Rubio JM, Guinart D, Kane JM, Correll CU. Early non-response to antipsychotic treatment in schizophrenia: a systematic review and meta-analysis of evidence-based management options. *CNS Drugs* 2023; **37:** 499–512.

57　Agid O, Schulze L, Arenovich T, et al. Antipsychotic response in first-episode schizophrenia: efficacy of high doses and switching. *Eur Neuropsychopharmacol* 2013; **23:** 1017–22.

58　Agid O, Arenovich T, Sajeev G, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *J Clin Psychiatry* 2011; **72:** 1439–44.

59　Stroup TS, McEvoy JP, Ring KD, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry* 2011; **168:** 947–56.

60　Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry* 2007; **164:** 415–27.

61　Heres S, Cordes J, Feyerabend S, et al. Changing the antipsychotic in early nonimprovers to amisulpride or olanzapine: randomized, double-blind trial in patients with schizophrenia. *Schizophr Bull* 2022; **48:** 1273–83.

62　Kahn RS, Winter van Rossum I, Leucht S, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry* 2018; **5:** 797–807.

63　Howes OD, McCutcheon R, Agid O, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry* 2017; **174:** 216–29.

64　Dong S, Schneider-Thoma J, Bighelli I, et al. A network meta-analysis of efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2024; **274:** 917–28.

65　Samara MT, Dold M, Gianatsi M, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. *JAMA Psychiatry* 2016; **73:** 199–210.

66　Masuda T, Misawa F, Takase M, Kane JM, Correll CU. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. *JAMA Psychiatry* 2019; **76:** 1052–62.

67　Vermeulen JM, van Rooijen G, van de Kerkhof MPJ, Sutterland AL, Correll CU, de Haan L. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1·1–12·5 years. *Schizophr Bull* 2019; **45:** 315–29.

68　Shah P, Iwata Y, Plitman E, et al. The impact of delay in clozapine initiation on treatment outcomes in patients with treatment-resistant schizophrenia: a systematic review. *Psychiatry Res* 2018; **268:** 114–22.

69　Wagner E, Siskind D, Falkai P, et al. Clozapine optimization: a Delphi consensus guideline from the treatment response and resistance in psychosis working group. *Schizophr Bull* 2023; **49:** 962–72.

70　Wagner E, Löhrs L, Siskind D, Honer WG, Falkai P, Hasan A. Clozapine augmentation strategies - a systematic meta-review of available evidence. Treatment options for clozapine resistance. *J Psychopharmacol* 2019; **33:** 423–35.

71　Northwood K, Pearson E, Arnautovska U, et al. Optimising plasma clozapine levels to improve treatment response: an individual patient data meta-analysis and receiver operating characteristic curve analysis. *Br J Psychiatry* 2023; **222:** 241–45.

72　Bjørndal N, Bjerre M, Gerlach J, et al. High dosage haloperidol therapy in chronic schizophrenic patients: a double-blind study of clinical response, side effects, serum haloperidol, and serum prolactin. *Psychopharmacology* 1980; **67:** 17–23.

73　Sakurai H, Suzuki T, Bies RR, et al. Increasing versus maintaining the dose of olanzapine or risperidone in schizophrenia patients who did not respond to a modest dosage: a double-blind randomized controlled trial. *J Clin Psychiatry* 2016; **77:** 1381–90.

74　Lindenmayer J-P, Citrome L, Khan A, Kaushik S, Kaushik S. A randomized, double-blind, parallel-group, fixed-dose, clinical trial of quetiapine at 600 versus 1200 mg/d for patients with treatment-resistant schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 2011; **31:** 160–68.

75　Vogel JS, van der Gaag M, Slofstra C, Knegtering H, Bruins J, Castelein S. The effect of mind-body and aerobic exercise on negative symptoms in schizophrenia: a meta-analysis. *Psychiatry Res* 2019; **279:** 295–305.

76　Cella M, Roberts S, Pillny M, et al. Psychosocial and behavioural interventions for the negative symptoms of schizophrenia: a systematic review of efficacy meta-analyses. *Br J Psychiatry* 2023; **223:** 321–31.

77　Cella M, Preti A, Edwards C, Dow T, Wykes T. Cognitive remediation for negative symptoms of schizophrenia: a network meta-analysis. *Clin Psychol Rev* 2017; **52:** 43–51.

78　Solmi M, Croatto G, Piva G, et al. Efficacy and acceptability of psychosocial interventions in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *Mol Psychiatry* 2023; **28:** 354–68.

79　Lejeune JA, Northrop A, Kurtz MM. A meta-analysis of cognitive remediation for schizophrenia: efficacy and the role of participant and treatment factors. *Schizophr Bull* 2021; **47:** 997–1006.

80　Sabe M, Zhao N, Crippa A, Kaiser S. Antipsychotics for negative and positive symptoms of schizophrenia: dose-response meta-analysis of randomized controlled acute phase trials. *NPJ Schizophr* 2021; **7:** 43.

81　Krause M, Zhu Y, Huhn M, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci* 2018; **268:** 625–39.

82 Németh G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet* 2017; **389:** 1103–13.

83 Helfer B, Samara MT, Huhn M, et al. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. *Am J Psychiatry* 2016; **173:** 876–86.

84 Galling B, Roldán A, Hagi K, et al. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World Psychiatry* 2017; **16:** 77–89.

85 Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Efficacy and safety/tolerability of antipsychotics in the treatment of adult patients with major depressive disorder: a systematic review and meta-analysis. *Psychol Med* 2023; **53:** 4064–82.

86 Kadakia A, Dembek C, Heller V, et al. Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. *BMC Psychiatry* 2021; **21:** 249.

87 Baldez DP, Biazus TB, Rabelo-da-Ponte FD, et al. The effect of antipsychotics on the cognitive performance of individuals with psychotic disorders: network meta-analyses of randomized controlled trials. *Neurosci Biobehav Rev* 2021; **126:** 265–75.

88 Bighelli I, Çıray O, Salahuddin NH, Leucht S. Cognitive behavioural therapy without medication for schizophrenia. *Cochrane Database Syst Rev* 2024; **2:** CD015332.

89 Moncrieff J, Crellin N, Stansfeld J, et al. Antipsychotic dose reduction and discontinuation versus maintenance treatment in people with schizophrenia and other recurrent psychotic disorders in England (the RADAR trial): an open, parallel-group, randomised controlled trial. *Lancet Psychiatry* 2023; **10:** 848–59.

90 Walburg FS, van Meijel B, Hoekstra T, et al. Effectiveness of a lifestyle intervention for people with a severe mental illness in Dutch outpatient mental health care: a randomized clinical trial. *JAMA Psychiatry* 2023; **80:** 886–94.

91 NICE. Metformin. 2024. https://cks.nice.org.uk/topics/diabetes-type-2/prescribing-information/metformin/ (accessed Sept 29, 2024).

92 Siskind D, Gallagher E, Winckel K, et al. Does switching antipsychotics ameliorate weight gain in patients with severe mental illness? A systematic review and meta-analysis. *Schizophr Bull* 2021; **47:** 948–58.

93 Marteene W, Winckel K, Hollingworth S, et al. Strategies to counter antipsychotic-associated weight gain in patients with schizophrenia. *Expert Opin Drug Saf* 2019; **18:** 1149–60.

94 Siskind D, Hahn M, Correll CU, et al. Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: a systematic review and individual participant data meta-analysis. *Diabetes Obes Metab* 2019; **21:** 293–302.

95 Bergman H, Walker D-M, Nikolakopoulou A, Soares-Weiser K, Adams CE. Systematic review of interventions for treating or preventing antipsychotic-induced tardive dyskinesia. *Health Technol Assess* 2017; **21:** 1–218.

96 Solmi M, Pigato G, Kane JM, Correll CU. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther* 2018; **12:** 1215–38.

97 Georgiou R, Lamnisos D, Giannakou K. Anticholinergic burden and cognitive performance in patients with schizophrenia: a systematic literature review. *Front Psychiatry* 2021; **12:** 779607.

98 Pringsheim T, Gardner D, Addington D, et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry* 2018; **63:** 719–29.

99 Praharaj SK, Kongasseri S, Behere RV, Sharma PSVN. Mirtazapine for antipsychotic-induced acute akathisia: a systematic review and meta-analysis of randomized placebo-controlled trials. *Ther Adv Psychopharmacol* 2015; **5:** 307–13.

100 Furukawa Y, Imai K, Takahashi Y, Efthimiou O, Leucht S. Comparative efficacy and acceptability of treatment strategies for antipsychotic-induced akathisia: a systematic review and network meta-analysis. *Schizophr Bull* 2024; sbae098.

101 Lu Z, Sun Y, Zhang Y, et al. Pharmacological treatment strategies for antipsychotic-induced hyperprolactinemia: a systematic review and network meta-analysis. *Transl Psychiatry* 2022; **12:** 267.

102 Labad J, Montalvo I, González-Rodríguez A, et al. Pharmacological treatment strategies for lowering prolactin in people with a psychotic disorder and hyperprolactinaemia: a systematic review and meta-analysis. *Schizophr Res* 2020; **222:** 88–96.

103 Taylor DM, Gaughran F, Pillinger T. The Maudsley practice guidelines for physical health conditions in psychiatry. Wiley-Blackwell, 2020.

104 Solmi M, Lähteenvuo M, Correll CU, Tanskanen A, Tiihonen J, Taipale H. Antipsychotic use and risk of low-energy fractures in people with schizophrenia: a nationwide nested case-control study in Finland. *Schizophr Bull* 2023; **49:** 78–89.

105 Taipale H, Solmi M, Correll CU, Tiihonen J. Relative risk of breast cancer associated with prolactin-increasing antipsychotic use. *J Clin Psychiatry* 2024; **85:** 23lr15135.

106 Siskind DJ, Wu BT, Wong TT, Firth J, Kisely S. Pharmacological interventions for smoking cessation among people with schizophrenia spectrum disorders: a systematic review, meta-analysis, and network meta-analysis. *Lancet Psychiatry* 2020; **7:** 762–74.

107 Petrakis IL, O'Malley S, Rounsaville B, Poling J, McHugh-Strong C, Krystal JH. Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. *Psychopharmacology* 2004; **172:** 291–97.

108 Taipale H, Tanskanen A, Tiihonen J. Safety of antipsychotic polypharmacy versus monotherapy in a nationwide cohort of 61889 patients with schizophrenia. *Am J Psychiatry* 2023; **180:** 377–85.

109 Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of antipsychotic polypharmacy *vs* monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry* 2019; **76:** 499–507.

110 Iqbal J, Wu H-X, Hu N, et al. Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. *Obes Rev* 2022; **23:** e13435.

111 Bak M, Campforts B, Domen P, van Amelsvoort T, Drukker M. Glucagon-like peptide agonists for weight management in antipsychotic-induced weight gain: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2024; **150:** 516–29.

112 Ueda P, Söderling J, Wintzell V, et al. GLP-1 receptor agonist use and risk of suicide death. *JAMA Intern Med* 2024; **184:** 1301–12.

113 Lähteenvuo M, Tiihonen J, Solismaa A, Tanskanen A, Mittendorfer-Rutz E, Taipale H. Repurposing semaglutide and liraglutide for alcohol use disorder. *JAMA Psychiatry* 2024; **82:** 94–98.

114 Kaul I, Sawchak S, Correll CU, et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. *Lancet* 2024; **403:** 160–70.

115 Anand R, Turolla A, Chinellato G, Sansi F, Roy A, Hartman R. Efficacy and safety of evenamide, a glutamate modulator, added to a second-generation antipsychotic in inadequately/poorly responding patients with chronic schizophrenia: Results from a randomized, double-blind, placebo-controlled, phase 3, international clinical trial. *Neuropharmacology* 2025; **266:** 110275.

116 Cao B, Cho RY, Chen D, et al. Treatment response prediction and individualized identification of first-episode drug-naïve schizophrenia using brain functional connectivity. *Mol Psychiatry* 2020; **25:** 906–13.

117 Sarpal DK, Argyelan M, Robinson DG, et al. Baseline striatal functional connectivity as a predictor of response to antipsychotic drug treatment. *Am J Psychiatry* 2016; **173:** 69–77.

118 Horowitz MA, Jauhar S, Natesan S, Murray RM, Taylor D. A method for tapering antipsychotic treatment that may minimize the risk of relapse. *Schizophr Bull* 2021; **47:** 1116–29.