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REVIEW

Finding the Right Setting for the Right Treatment During the Acute Treatment of Individuals with Schizophrenia: A Narrative Review and Clinical Practice Guideline

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Background: Schizophrenia is most times a chronic and often debilitating illness associated with poor mental health outcomes. Early and effective treatment of schizophrenia in the most appropriate setting can make a significant difference in the long-term recovery. The aim of this narrative review was to provide suggestions and recommendations for effectively managing patients with schizophrenia during acute exacerbations and to enhance awareness and skills related to personalized medicine.

Methods: A panel of academics and clinicians with experience in the field of psychosis met virtually on July 13th 2023 to narratively review and discuss the research evidence and their clinical experience about the most appropriate acute treatments for patients with schizophrenia. This manuscript represents a synthesis of the panel analysis and discussion.

Results: First contact is very important for service users, as is finding the most adequate treatment setting. If patients present to the emergency department, which may be a traumatic setting for service users, a dedicated environment with adequate space and specialized mental health support, including personnel trained in de-escalation techniques, is recommended. A well-connected continuum of care is strongly recommended, possibly with seamless links between inpatient units, day hospital services, outpatient facilities and rehabilitation services. Ideally, this should be structured as part of a coordinated step-down service line. Treatment challenges include suboptimal response, side effects, and nonadherence, which is reduced by the use of long-acting injectable antipsychotics.

Conclusion: Individual circumstances, including age, gender, and presence of hostility/aggression or self-harm, cognitive impairment and negative symptoms, comorbidities (depression, substance use disorders) or associated symptoms (anxiety, insomnia), should be considered when selecting the most appropriate treatment for the acute phase of schizophrenia. Efficacy and feasibility, as well as acceptability and tolerability of treatments, require joint consideration from the early stages of schizophrenia, thereby enhancing the possibility of improved short- and long-term outcomes.

Keywords: schizophrenia, first-episode psychosis, acute setting, clinical care

Background

Schizophrenia is most times a chronic and often debilitating illness that is associated with positive, negative and cognitive symptoms, impaired reward processing and illness insight, as well as poor functional and physical health outcomes.[1–3]

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Although genetic and environmental factors have been implicated, including maternal infection due to seasonal birth findings,[4] the pathophysiology of schizophrenia remains to be elucidated, and valid biomarkers are lacking.[5] The median age at the onset of schizophrenia and schizophrenia-spectrum disorders (first-episode psychosis) is 20.5 years.[6] All-cause mortality is increased in people with schizophrenia compared to the general population with the greatest risk in first-episode (RR = 7.4) and incident (ie, earlier-phase) schizophrenia (RR = 3.5), with suicide being the biggest relative risk factor compared to the general population.[7]

Early-onset schizophrenia (EOS) refers to the development of a first schizophrenia episode before the age of 18 years.[8] EOS is associated with poor outcome: in fact, 3/5 individuals with EOS had poor functioning (GAF: ≤50) at follow-up.[9] Furthermore, EOS is associated with more neurodevelopmental difficulties,[10] poorer premorbid adjustment,[11] as well as more negative symptoms[12] and higher impulsivity,[13] among other relevant outcomes, than adult-onset schizophrenia (AOS). A challenge in the care of these patients is the difficulty in obtaining adequate transitional care for adult services.[14]

The timing and manner in which the treatment of individuals with schizophrenia is managed in the acute phase has both short-term and long-term implications for individuals with EOS and AOS.[15,16] Indeed, it is known that there is an association between delays in psychosis treatment – called duration of untreated psychosis or DUP – and poor outcomes.[17] Furthermore, shared decision-making at this point is key to the patient's further illness development.[18,19] Previous narrative and systematic reviews have examined the pathways to mental health care for people with first-episode psychosis and factors that may predict relapse and acute exacerbation of psychotic symptoms in people with schizophrenia.[17,20–23] A review found that the first contact for the largest proportion of patients was a physician and that the referral target for the largest proportion of patients was the emergency department.[24] The most common first contacts to seek help appeared to be family members or relatives (26.7%), close friends (17.9%), psychiatrists in private practice (14.4%), and general practitioners (12.2%).[22] Another review found that greater antipsychotic efficacy was associated with higher baseline total symptom severity, treatment-naive/first-episode status, shorter illness duration, and lower placebo effect.[23] In addition, factors associated with better outcomes in people with schizophrenia included absence of substance abuse comorbidity, greater early treatment response, better antipsychotic adherence, and fewer relapses.[17,20,21] While previous expert consensus groups have evaluated specific parts of the treatment pathway for people with schizophrenia, including the role of long-acting injectable antipsychotics in schizophrenia,[25–28] no expert opinion has focused on the importance of finding the right setting and treatment for people with an acute psychotic episode. The aim of this study was to provide suggestions about the most appropriate management of acutely exacerbated patients with schizophrenia and to increase the awareness and skills regarding personalized medicine in the management of patients with acute schizophrenia, ultimately aiming to enhance the chance of positive outcomes from the early beginning of the treatment journey.

Methods

Design: Narrative Review and Clinical Practice Guideline

A group of senior academics and clinicians with extensive experience in the field of psychosis (ie, the co-authors in the author line) met virtually on July 13, 2023. These experts represented both inpatient and outpatient as well as research settings, children, adolescents, adults and the elderly, as well as experience in the clinical care of patients with psychotic disorders in several countries, including Germany, Italy, Spain, UK and the USA. During this meeting, participants discussed and synthesized proposals for the acute treatment of people with schizophrenia, shared their research and clinical experiences, and offered suggestions for advancing knowledge in the field and improving clinical care. Published literature and scientific evidence relevant to the acute management of people with schizophrenia were critically reviewed.

This manuscript represents a narrative review of information from individual presentations, collective discussions, a comprehensive review of the evidence, and feedback from all panel members. During the development of this manuscript, all members provided critical and constructive feedback on at least two occasions.

The first part of the manuscript focuses on finding/creating the right treatment setting, looking at the role of emergency departments as well as hospital inpatient units and community settings. The second part focuses on strategies for finding the right treatment through stratified and personalized medicine approaches, addressing the challenges of identifying the right treatment-patient match.

Results

Finding the Right Setting

First contact is very important for service users. In the first year after diagnosis, the incidence of treatment discontinuation is significant, reaching 30 events per 100 participant-years.[29] To find the right setting, environmental and family factors should be taken into account.

It should be noted that sometimes the first contact may be in the context of pre-existing physical health problems and the patient may already be at the hospital. Other times, patients may be seeking help for other mental health conditions (eg, anxiety disorders). In these cases, it is particularly important to avoid misdiagnosis and mistreatment. In all cases, it is important to consider the patient's preferences (Figure 1)

Emergency Department

When patients arrive at the emergency department, there is an early triage process that affects patient flow. The emergency department (ED) as the point of entry into psychiatric care is often perceived by service users with schizophrenia as the most traumatic setting. However, the experience can be improved if the ED meets certain conditions (Figure 2 provides a hierarchy of ED elements and service provision).

Challenges to finding the right accommodations include (1) privacy, (2) safety, (3) ability to provide a timely assessment, (4) catchment area covered and location of on-call psychiatrist, (5) differences between public and private sectors, including difficulties with insurance coverage, (6) ambulances taking patients to the wrong hospital and inability to provide the appropriate treatment, (7) lack of specialized staff, including psychiatric nurses and social workers, and (8) need for isolation and associated procedures to ensure patient and staff safety.

Strategies and recommendations for patients to have a good experience in the ED include[30] a) a dedicated environment with adequate space, b) specialized mental health nurses to support individuals while in the ED, c) consideration of direct admission to the inpatient unit if indicated by the community psychiatrist, if available, d) continuity of treatment provider across settings if available, e) training in de-escalation techniques (see ten domains of de-escalation and associated recommendations for the acute phase of schizophrenia in Table 1), and f) use less invasive rapid acting treatments than short-acting intramuscular antipsychotics and/or benzodiazepines for agitation and aggression, such as oral benzodiazepines and inhaled loxapine or sublingual dexmedetomidine, when indicated and available. Patients with schizophrenia require a comprehensive physical examination, including blood and drug tests, especially if physical

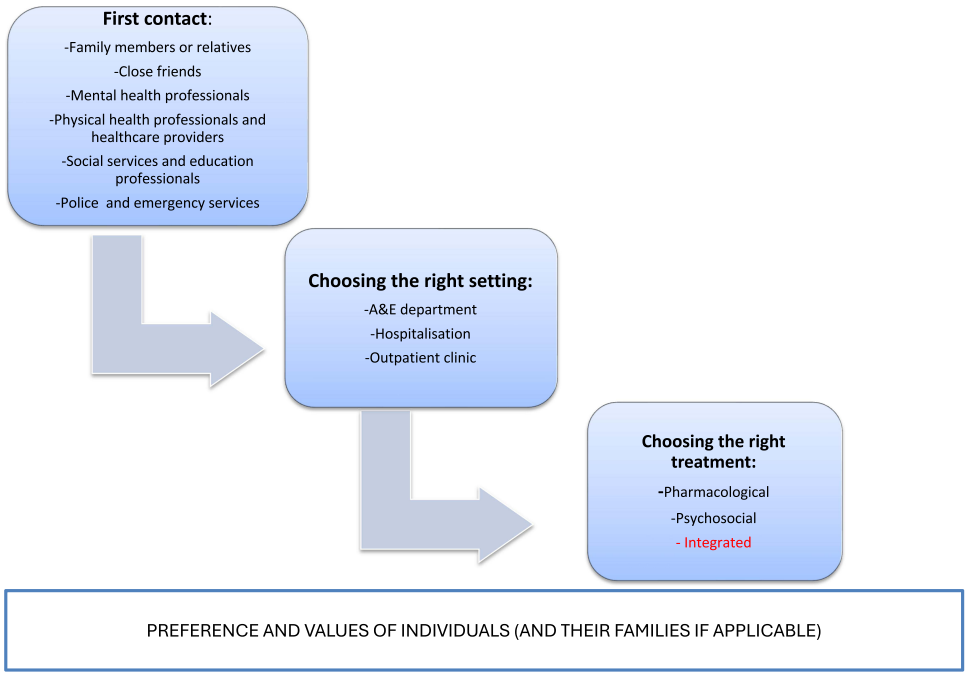

Figure 1 Pathways to care and treatment.

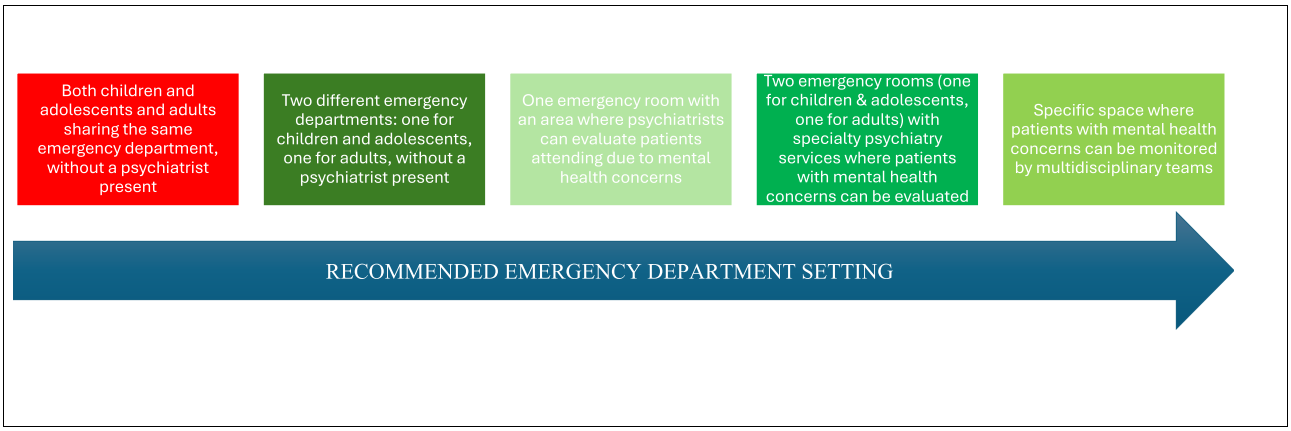

Figure 2 Emergency Department provisions available.

illness and/or substance use is suspected. In cases with rapid onset psychosis and/or neurological signs, further tests, including brain imaging and lumbar puncture, may be indicated. The emergency department may be the most appropriate place to perform these tests.

Table 1 Ten Domains of De-Escalation and Recommendations

Domains of De-Escalation
1. Respect personal space.
2. Do not be provocative.
3. Establish verbal contact.
4. Be concise.
5. Identify wants and feelings.
6. Listen closely to what the patient is saying.
7. Agree or agree to disagree.
8. Lay down the law and set clear limits.
9. Offer choices and optimism.
10. Debrief the patient and staff.
Recommendations from experts in schizophrenia.
1. Always ask for permission before making physical contact.
2. Be aware that depending on previous experiences and the content of delusional ideation, actions may be perceived differently to expected.
3. Avoid physical contact or getting closer to the individual without anticipation or permission.
4. Avoid non-literal or sarcastic language.
5. If unsure directly ask about feelings and desires.
6. If unsure, double check understanding with the patient.
7. Avoid unhelpful discussions about who is right or wrong.
8. Offer to help with what you can and if not possible offer to listen.
9. Ensure that although in a certain moment choices may be limited, the situation may change in the future.
10. Ensure appropriate training in de-escalation techniques.

Notes: Data from Højlund et al.[31]

Hospitalisation vs Community Treatment

Hospitalization may be necessary in some contexts because of the need for medical or psychiatric evaluation and management, including safety concerns in the acute treatment of schizophrenia.

Reasons for hospitalization include assisting clinicians in conducting multiple tests for complex disorders and appropriately managing the risk of self-harm, aggression, or major disorganization. Of note, some studies suggest that patients discharged too soon are more likely to discontinue treatment[29] and more likely need to be re-admitted,[32] according to some studies. Admission may provide time to work with family members and caregivers and to provide psychoeducational strategies, as well as to liaise with social services and to refine the diagnosis. There are also reasons to support discharge. Indeed, according to other studies, hospitalization may contribute to a greater risk of poor adherence.[33] In any case, hospitalization is often perceived as coercive. There may also be increased pressure to discharge due to a lack of beds.

Good outpatient care and community resources, including day hospital rehabilitation units that allow for safe discharge, ideally as part of a coordinated step-down approach to care in the least restrictive environment, are recommended. We suggest that an appointment should be arranged from the hospital with the community psychiatrist (or the same psychiatrist if the facility is affiliated), as well as with the general practitioner (who may continue to prescribe medication in some countries) and specialized mental health nurses where available.

The length of hospitalization varies between and within countries, depending on resources, the ratio of beds to catchment area, and the reimbursement system.

- In Italy, there is considerable variation within the same country. In some hospitals (eg, University of Siena Medical Center), the average length of stay in an inpatient unit is as short as 5–6 days, after which patients are immediately transferred to a day hospital for further care and rehabilitation, and then to outpatient care. In most hospitals, however, the length of stay in an inpatient unit is about 12 days, after which patients are transferred to community care, outpatient and rehabilitation treatment centers. For children and adolescents, the length of hospital stay varies widely across the country, mostly depending on the number of available inpatient beds, which are usually very limited.
- In Spain, the average length of stay in inpatient units is 2–3 weeks. There are no differences in length of stay between children and adolescents and adults.
- In Germany, on the other hand, the length of hospitalization for adults is about 3–4 weeks, while for children and adolescents, the length of admission to psychiatric units may increase to 2–3 months (at least in university settings).
- In United Kingdom, the length of hospitalization for adults is typically longer than a month. In children and adolescents, it can be even longer and often discharge meetings with families and social services are arranged during hospitalization.
- The authors provide their expertise on the acute treatment of people with schizophrenia in their respective countries, but research and evidence coming from other countries (eg, equatorial regions or Asian countries)[34] is important.

An important point is that certain conditions need to be met to facilitate safe discharge (Figure 3). Psychometric instruments can help assess whether individuals are ready for discharge. For example, the Readiness for Discharge Questionnaire (RDQ)[35] assesses six items: suicidality/homicidality, control of aggression/impulsivity, activities of daily living, medication use, delusions/hallucinations interfering with functioning, and global status.

Finding the Right Treatment

General principles for finding the right treatment include establishing an appropriate and personalized treatment plan based on the patient's diagnosis, comorbidities, previous treatment response and tolerability, adherence patterns, and preferences. A respectful and humane approach is recommended, as well as shared decision-making and motivational interviewing approaches. It is important to choose treatment adequately from the start and to consider switching in case

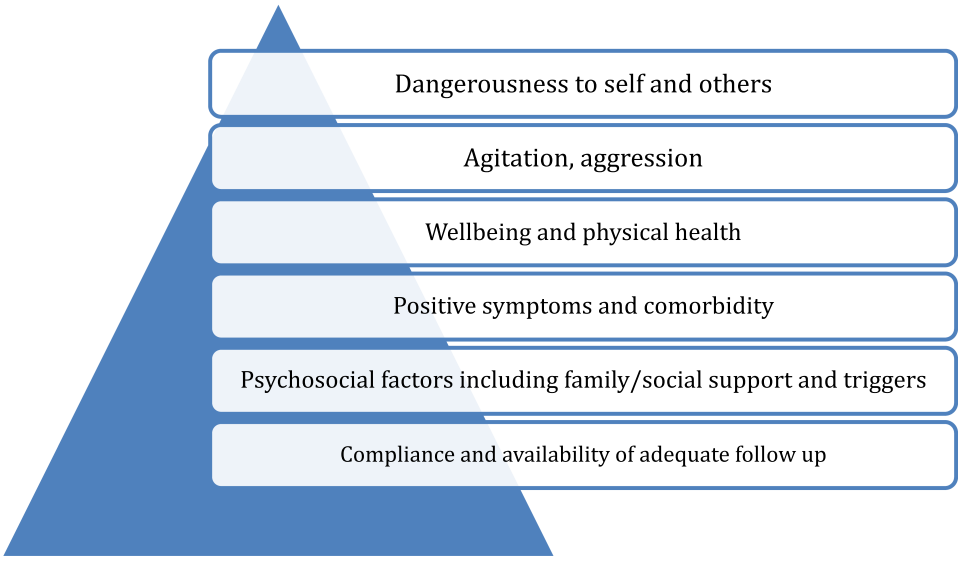

Figure 3 Factors to be addressed and hierarchy of needs in order to discharge patients with schizophrenia.

of early non-response.[36] Treatment approaches that can positively influence the patient's "fate" of treatment engagement and response should be *feasible (in terms of access and adherence); *acceptable (taking into account patient preferences); *tolerable (associated with few or minimal side effects); and *efficacious (associated with good response and outcomes) (FATE).

Clinical practice guidelines recommend antipsychotic monotherapy for psychosis as a first and second step.[37] Medications that are recommended and used long term are often not used acutely. This discontinuous approach affects acceptability and tolerability on the patient side and creates hesitancy to change a treatment regimen initiated on an inpatient service that helped stabilize and discharge the patient, on an outpatient care provider side. One option is to use non-sedating/less sedating, more tolerable antipsychotics acutely and if needed use those in combination with benzodiazepines, or choosing a sedating antipsychotic when rapid action and sedation are needed. Thereafter, the benzodiazepines or sedating antipsychotic can be tapered and the patient be discharged on the non-sedating/less sedating and more tolerable antipsychotic. Alternatively, one could start with a sedating antipsychotic but switch to a less sedating antipsychotic after initial response or if intolerance occurs. However, many troublesome side effects can accumulate over time, and once a medication has begun to work and is effective, clinicians are often reluctant to switch antipsychotics and possibly risk losing the initial response. When side effects or lack of efficacy become apparent, a switch to another medication should be considered. Nonpharmacologic strategies should be added as and when appropriate.

According to a recent network meta-analysis, most antipsychotics reduced total symptoms in acutely ill patients with schizophrenia more than placebo, with the highest effect size for clozapine (standardized mean difference–SMD=0.89). SMDs compared with placebo for reduction of positive symptoms were highest for amisulpride (SMD = 0.69), and for negative symptoms for clozapine (SMD = 0.62)[38] However, in acutely exacerbated populations with prominent positive symptoms, it is not possible to clarify whether improvements in negative symptoms were related to primary or secondary negative symptoms.[39] In a study of adults with predominant negative symptoms, cariprazine was superior to risperidone for negative symptoms, functionality and global illness severity.[40] Treatment discontinuation varied between antipsychotics (risk ratio from RR = 0.52 for clopenthixol to RR = 1.15 for pimozide).[38]

In contrast to generally smaller and more "gradual" (ie, nonsignificant) differences in efficacy in meta-analyses, differences in adverse effect liabilities are generally larger, statistically significant and also more predictable. Mean differences from placebo for weight gain ranged from −0.16 kg for ziprasidone to 3.21 kg for zotepine, while prolactin elevation ranged from partial dopamine agonists being prolactin-neutral to 48.51 ng/mL for paliperidone.[38] In general,

some medications seem to be better tolerated in the long term (lurasidone; aripiprazole; brexpiprazole; cariprazine, lumateperone),[41] in agreement with our expert opinion. Of note, antipsychotic use is protective against mortality compared with no antipsychotic use (RR = 0.71), with the largest effects for second-generation injectable long-acting antipsychotics (SGA-LAIs) (RR = 0.39), clozapine (RR = 0.43), any LAI (RR = 0.47), and any second-generation antipsychotic (RR = 0.53).[42]

Personalised Medicine

Several factors and individual circumstances need to be considered when deciding on the appropriate treatment for the acute phase of schizophrenia. Relevant factors include sociodemographic factors, such as age or gender, predominance or severity/functional impact of specific symptoms (positive symptoms, hostility/aggressive behaviours, self-harm/suicidal behaviours, negative symptoms, affective symptoms, cognitive symptoms), and comorbidities (depression, substance use disorders) or associated symptoms (anxiety, insomnia) (see Table 2).

Below are some recommendations for some relevant sociodemographic and clinical factors:

a) Children and adolescents: Brain development is relevant to symptom expression and treatment response in children and adolescents.[43] Sometimes lower antipsychotic doses and/or slower titration are required in EOP. Note that many medications are prescribed off-label in paediatric populations; insurance companies may or may not pay for certain medications, which is important to know. Prescribers may need to seek approval from local insurance companies. In any case, more research studies are needed to make more medications available on-label for youth with schizophrenia (and other mental disorders). Aripiprazole, brexpiprazole, lurasidone, and risperidone are recommended by the panellists as on-label treatments for EOS with a more benign side effect profile. For children and adolescents with treatment-resistant schizophrenia, clozapine is recommended.[44]
b) Sex: Prolactin-raising antipsychotics should be avoided in females. Long-term exposure to prolactin-increasing, but not prolactin-sparing, antipsychotics (including clozapine, quetiapine, or aripiprazole) has been associated with an increased risk of breast cancer.[45] Of note, some side effects (eg, gynecomastia, erectile dysfunction) may be associated with discomfort/decreased quality of life in males; amenorrhea can be associated with distress and osteoporosis in females; and galactorrhea, decreased libido and anorgasmia can decrease quality of life in both males and females.[46,47]
c) Presence of hostility/aggression or self-harm: Safety is a major concern in the acute treatment setting for many patients with schizophrenia. Staff should be trained in non-pharmacologic de-escalation techniques that should be used early and widely as much as possible.[30] Adequate space should be available. Sedation may need to be added temporarily to ideally ultimately non-sedating, non-weight gain producing antipsychotics, utilizing targeted and time-limited benzodiazepine or sedating antipsychotic cotreatment. Short-acting injectable antipsychotics should

Table 2 When a Patient Arrives with a First Psychotic Episode (FEP) the Treatment Depends on

Predominance of Clinical Symptoms	Other Factors
Positive symptoms	Age
Negative symptoms	Sex
Cognitive symptoms/ impairment	Metabolic syndrome or risk of developing metabolic syndrome
Affective symptoms	Social support
Residual symptoms	Family or personal history of response to treatment
Catatonic symptoms	Presence of comorbidities (mental health, physical health)
Suicidal behaviours	Presence of substance abuse and type of substance
Aggressive behaviours	Other predictors of conversion to bipolar disorder or schizophrenia

be utilized as a last resort alternative, and second-generation antipsychotics are preferrable from a side effect perspective.[30,48,49]

d) Predominance of cognitive symptoms: In an acute episode, the degree of cognitive impairment may be difficult to assess (one would have to rely on informant reports), and in some cases, safety must be prioritized in the acute setting. When possible, it is recommended to avoid sedating and anticholinergic medications and medications that may cause extrapyramidal symptoms and worsen cognitive deficits.[50] The differences between antipsychotics are not entirely clear.[51] One study suggested that lurasidone may be better than quetiapine for cognitive symptoms.[52] Benzodiazepines and anticholinergics for the treatment of parkinsonian side effects should be avoided in the long term. Cognitive remediation[53–55] and aerobic exercise[56,57] have shown benefits, but availability and adherence/persistence can be an issue. Social skills training is recommended, as is cognitive remediation, for patients who also have cognitive impairment associated with schizophrenia.[53–55] For both cognitive remediation and exercise interventions, availability and adherence may be difficult.

e) Predominance of negative symptoms: Medications that produce sedation and extrapyramidal symptoms may themselves produce secondary negative symptoms.[58] These medications should therefore be avoided. According to EPA guidelines, based on meta-analytic evidence,[59,60] the addition of antidepressants to antipsychotic treatment should be considered in people with negative symptoms secondary to depression or in people with negative symptoms that are resistant to antipsychotics. However, no pharmacological treatment has been shown to be effective for primary persistent negative symptoms with low-dose amisulpride and cariprazine coming closest to this aim.[61]

f) Presence of insomnia: Various therapeutic options should be considered, especially non-pharmacological strategies. Benzodiazepines may be considered in the short term. Quetiapine may also be considered, although not in the long term, due to the risk of cardiovascular side effects, even at low doses.[62,63]

g) Post-psychotic depression: The antidepressant effect typically decreases with higher doses of antipsychotics that lead to more postsynaptic dopamine receptor blockade. It should be noted that the antidepressant effect of lurasidone is also present at higher doses, which is an advantage. An antidepressant may need to be added, often after the acute episode. Psychosocial strategies and psychological interventions may also be considered (eg, cognitive behavioral therapy).

Challenges for Finding the Right Treatment and Recommendations

A) Risk of discontinuation: 61% of individuals appear to have difficulty with consistent adherence over a 4-year period. Adherence problems appear to be associated with younger age, non-white race, and concomitant substance use.[33] Medications with fewer side effects (eg, less sedation) are recommended[64] (adverse effect profiles of selected antipsychotic drugs can be found in Table 3).

Benzodiazepines may be added temporarily to allow safe antipsychotic initiation. People with schizophrenia are 67% less likely to discontinue treatment with long-acting injectable antipsychotics than with oral antipsychotics.[29] Benefits of LAIs over oral antipsychotics in preventing hospitalization or relapse have been found in settings ranging from limited research (eg, randomized clinical trials) to real-world settings.[66] In fact, clinical practice guidelines recommend the use of long-acting injectable antipsychotics (LAIs) in schizophrenia, mainly in cases of nonadherence (77.8%), maintenance treatment (72.2%), or when patients prefer this treatment (66.7%).[37] However, proactive and preventive LAI prescribing may yield even better results.[67,68]

B) Suboptimal response at current antipsychotic dose and side effects associated with dose escalation: All continuation strategies appear to be more effective in preventing relapse than discontinuing antipsychotic treatment, with a large risk reduction for continuation at standard doses (RR = 0.37) and antipsychotic switching (RR = 0.44) and a moderate risk reduction for dose reduction (RR = 0.68). Antipsychotic continuation and switching did not differ significantly in relapse prevention, whereas antipsychotic dose reduction was outperformed by both continuation and switching.[69] A trial comparing standard versus reduced antipsychotic doses for relapse prevention in multi-episode schizophrenia found that reduced doses increased the risk of relapse and all-cause discontinuation.[31]

Table 3 Adverse Effect Profiles of Selected FGA and SGA Drugs

Adverse Effect	Mechanism	Dose/ Titration Dependent	AMI	ARI	ASE	BRE	CAR	CLO	ILO	LUR	OLA	PALI	QUE	RIS	SER	ZIP	*CPZ*	*HAL*	*LOX*	*PER*
Sedation	H1 blockade	+++	0/+	0/+	+	0/+	0/+	+++	0/+	+/++	+/++	0/+	++ [b]	+	0/+	+	+++	+	+	+
Cognitive impairment	Anti- cholinergic, D2 blockade	++	+	0	+	0	0	+	0	0	+	+	+	+	+	0	++	++	++	++
Weight Gain [a]	H1, D2, 5HT2c blockade	0/+	0/+	0	+	0	0/+	+++	+/++	0/+	+++	++	++	++	++	0/+	+++	+	+	++
Metabolic syndrome	Weight gain, over-eating, direct effects	0/+	0/+	0/+	0/+	0/+	0/+	+++	+	0/+	+++	+	++	+	+	0/+	+++	*0*/+	+	+
Acute Parkinsonism	D2 blockade	+++	+	+	++	+	++	0	0/+	++	0/+	++	0	++	0/+	+	+	+++	++	++
Akathisia	D2 blockade and, α, 5HT interaction	+++	+	++	+	++	++	+	0/+	+/++	+	+	+	++	+	+/++	+	+++	++	++
Tardive Dyskinesia	D2 receptor desensitization	++	0/+	0/+	0/+	0/+	0/+	0	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	++	+++	++	++
Withdrawal Dyskinesia	D2 blockade rebound	+++	+	+/++	+	+/++	+/++	0	+	+	0/+	+	0/+	+	0/+	+	*0*/+	++	+/++	+/++
Seizures	D2 blockade?	+++	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	+	0/+	0/+	*0*/+	*0*/+	*0*/+	*0*/+
↑ QTc interval	Cardiac ion channel effects	++	++	0	+	0	0	+	0/+	0/+	+	+	+	++	++	++	+	++	+	+
Hypotension	α1 blockade	+++	0/+	0/+	+	0/+	0/+	+++	+++	0/+	++	+	++ [b]	++	+	++	+++	++	+	++
Cardiovascular events (myocardial infarction, stroke)	Hyper-coagulability, metabolic effects, direct channel toxic action	+	0/+	0/+	+	0/+	?	++	?	?	++	+	++	+ +	0/+	+	++	++	+	++
Sialorrhea	M4 agonism	+	0	0	0	0	0	++	0	0	0	0	0	0	0	0	*0*	*0*	*0*	*0*
Neutropenia	Direct effect	+	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	+	*0*/+	*0*/+	*0*/+
↑ Prolactin/ sexual dysfunction	D2 blockade	+++	+++	0	+	0	0	0	0/+	+	+	+++	0	++ +	+	+	+	+ +/+ ++	++	++
Myocarditis and cardiomyopathy	Unknown	0	0	0	0	0	0	++	0	0	0	0	0/+	0	0	0	*0*	*0*	*0*	*0*
Pneumonia and acute respiratory failure	Sialorrhea, central sedation, muscle impairment	+++	+	0	0	0/+	0/+	++	0/+	0/+	+	0/+	0/+	+	0/+	0	+	+	+	+
Gastrointestinal adverse effects (eg nausea, vomiting, diarrhea, constipation)	Anti- Cholinergic, D2 agonism	+	0	+	0	+	+	++	0	0	++	0	0	0	0	0	++	*0*	++	++
Pulmonary embolism and venous thromboembolism	Hyper-coagulability	0/+	+	0/+	+	?	?	+	?	?	+	+	+	+	0/+	0/+	++	+	+	++
Dry mouth, dental caries	Anti- cholinergic	+	0	0	0	0	0	++	0	0	++	0	++	0	0	0	++		++	++

(*Continued*)

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Table 3 (Continued).

Adverse Effect	Mechanism	Dose/ Titration Dependent	AMI	ARI	ASE	BRE	CAR	CLO	ILO	LUR	OLA	PALI	QUE	RIS	SER	ZIP	*CPZ*	*HAL*	*LOX*	*PER*
Liver dysfunction	Metabolic syndrome, direct effect	0/+	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	+	0	+	+	0/+	0	++	*0/+*	*0/+*	*0/+*
Urinary and kidney function	Anti-cholinergic (Prolactin)	++	+	0	0	0	+	+	0	+	+	0	0	0/+	0	0/+	+	*0*	*0*	+
Osteopenia, osteoporosis and fractures	D2 blockade (prolactin)	+	+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	+	0/+	+	0/+	0/+	*0/+*	+	*0/+*	*0/+*
Binge eating, impulse control disorder, gambling	H1 blockade, D2 agonism	+	0	+	+	?	?	++	0	0	++	+	0	+	0	0/+	+	*0*	*0*	*0*
Sexual and reproductive system dysfunction	D2 blockade (Prolactin), α blockade, anti-cholinergic	++	+	0/+	+	?	0	++	?	+	++	++	+	++	+	0/+	++	++	++	++
Endocrine adverse effects (diabetes ketoacidosis, hypothyroidism, and hyponatremia).	Unknown	0/+	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	++	0/+	0/+	++	0/+	0/+	*0/+*	*0/+*	*0/+*	*0/+*
Hyperprolactinemia	D2 blockade	+++	+++	0	+	0	0	+	+	++	+	+++		++ +	++	++	+	+++	+	+
Breast and cervical cancer	Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	*0*	*0*	*0*	*0*
Malignant neuroleptic syndrome	Unknown	++	0/+	0/+	0/+	?	?	+++	?	?	+	0/+	+	+	+	+	+++	+++	+	+

Notes: Reproduced from Solmi M, Murru A, Pacchiarotti I, et al. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. *Ther Clin Risk Manag*. 2017;13:757-777.[65]
Abbreviations: AMI, amisulpride; ARI, aripiprazole; ASE, asenapine; BRE, brexpiprazole; CAR, cariprazine; CLO, clozapine; ILO, iloperidone; LOX, loxapine; LUR, lurasidone; OLA, olanzapine; PALI, paliperidone; QUE, quetiapine; RIS, risperidone; SER, sertindole; ZIP, ziprasidone; CPZ, chlorpromazine; HAL, haloperidol; MOL, molindone; PER, perphenazine.

Several strategies have been proposed to address the challenge of suboptimal treatment response. Increasing the dose to the maximum dose in the summary of product characteristics may be indicated if the positive symptom response is partial and there are no side effects,[36] but doses above the approved dose range have not been shown to increase treatment response.[65] However, increasing the dose of antipsychotics because of persistent negative, affective, or cognitive symptoms should be avoided because the chances of improving these symptoms are low. Instead, other strategies should be considered.

Evidence for combination strategies is limited to pharmacological interventions. One study found that total PANSS scores improved significantly at eight weeks in the amisulpride plus olanzapine group compared with the olanzapine plus placebo group (d = 0.396).[70] However, at eight and sixteen weeks, sexual dysfunction, weight, and waist circumference increase were significantly higher in patients receiving amisulpride plus olanzapine than in those receiving amisulpride plus placebo, with no differences in serious adverse events.[70] After failing to achieve remission on amisulpride, switching to olanzapine did not improve outcomes.[71] Switching to clozapine, on the other hand, has been shown to be beneficial (even after a failure in a single antipsychotic trial).[42,71,72]

Other augmentation strategies that may be considered include the addition of an antidepressant[59,60] or a partial dopamine agonist[73] for negative symptoms. Benzodiazepines and second-generation antipsychotics may also be considered for agitation (see above). As mentioned above, there is limited evidence regarding pharmacological agents for cognitive symptoms. Cognitive remediation, exercise, and social skills training may be recommended.[39]

Combining pharmacological and psychological interventions is recommended. Early *intervention* services providing a combination of pharmacological and psychosocial interventions are associated with an improvement in clinical and functional outcomes.[74] Cognitive remediation therapy and cognitive behavioural therapy can improve psychosocial functioning in some patients.[75,76] Psychoeducation interventions and family interventions, on the other hand, can improve negative symptoms and decrease visits to emergency departments in early psychosis[77] and reduce relapses in adults.[76] Electroconvulsive therapy may be considered as well.[78] Current indications include treatment resistance, pharmacotherapy augmentation, catatonia, suicidal behavior and severe agitation.[79]

Conclusions

Clinicians should work hard to find the right setting and the right treatment for their patients with schizophrenia from the acute phase onwards. A dedicated environment with adequate space is needed in emergency departments, as well as specialized mental health support. Good outpatient care and community resources, including rehabilitation units and day hospitals that allow for safe discharge, ideally as part of a coordinated step-down approach to care in the least restrictive environment, are recommended. Individual circumstances need to be considered when selecting the most appropriate pharmacologic and non-pharmacologic treatments for the acute phases of schizophrenia. Relevant factors include sociodemographic factors, such as age or gender, predominance of symptoms (positive symptoms, hostility/aggressive behaviours, self-harm/suicidal behaviours, negative symptoms, affective symptoms, cognitive symptoms), and comorbidities (depression, substance use disorders) or associated symptoms (anxiety, insomnia). Efficacy and feasibility, as well as acceptability (including patient preferences) and tolerability, must be considered at an early stage to increase the chance of enhanced outcomes.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

Our study did not involve experiments on humans or the use of human tissue samples. Patients were not involved; the evidence and previously published literature on the field that is reviewed by the group of senior academics.

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