The current role of first-generation antipsychotics Recommendations Report

Meeting objectives

- Obtain insights from an international panel of experts on how first-generation antipsychotics (FGAs) can be used most effectively in clinical practice.
- Develop and circulate a report detailing key recommendations from the expert panel, to guide the use of FGAs in clinical practice.
- Ultimately improve the quality of care for patients who need treatment with antipsychotics.

Advisors

Prof. Pierre-Michel Llorca
Professor of Psychiatry, Université Clermont Auvergne, France

Prof. Göran Hajak
Professor of Psychiatry, University of Regensburg, Germany

Dr Anna Mané
Psychiatrist, Hospital del Mar-Parc de Salut MAR, Spain

Prof. Giulio Perugi
Professor of Clinical Psychiatry and Psychopharmacotherapy, University of Pisa, Italy

Executive summary

- The advisory board meeting was attended by four experts in psychiatry from around Europe. This report summarises the discussions from the meeting and reflects the views and experiences of the advisors; recommendations may not reflect the views and experiences of others.

- There is a general belief across Europe that SGAs are safer than FGAs and are preferred as antipsychotic therapy in many situations.

- Younger (aged <50) neurologists/psychiatrists generally have poor knowledge about FGAs and their uses; they have little practical experience of treating patients with FGAs.

- However, experienced clinicians are aware of how FGAs can be used effectively, based on the individual properties of each drug.

- In practice, the distinction between FGAs and SGAs is not clear-cut, even in countries such as Italy where guidelines make a clear distinction (SGAs are recommended for first-line therapy, FGAs for second-line therapy).

- FGAs are mostly used in specific settings and patient populations:

    - The majority of FGA use occurs in emergency and acute settings, to reduce symptoms of agitation and delirium.

    - Long-acting injectable FGAs are added to SGAs in treatment-resistant schizophrenia.

    - Long-acting FGAs are used in cases where adherence to therapy is a concern.

    - FGAs administered in drops are useful for patients who have difficulties swallowing pills, e.g., patients with dementia.

    - Off-label prescription of FGAs by general practitioners (GPs) is increasingly common to sedate patients with non-specific conditions like stress, burnout and insomnia.

- The general belief that FGAs are inferior to SGAs is based on the higher risk of extrapyramidal symptoms (EPS) with FGAs. However, SGAs carry an increased risk of metabolic side effects. Although these side effects can be as harmful as EPS, they have a slower onset and are less of an immediate concern among treating clinicians.

- In addition, doses used to compare FGAs and SGAs are often widely different, the higher doses accounting for, at least in part, the greater incidence of side effects observed with FGAs. The effects of different doses of antipsychotics should be included in medical education initiatives to address the current unbalanced perception about FGAs and SGAs.

- The current focus is on the risk of EPS associated with FGAs, and many doctors avoid prescribing FGAs for fear of these side effects. However, the risk of metabolic side effects with SGAs poses an equally important health risk for certain patients, which is largely overlooked in decision-making.

- Generally, there is a need to improve education on antipsychotic therapies:

    - to raise awareness of FGAs among young clinicians who have received little education about these products.

    - to disseminate knowledge obtained by clinicians with experience of prescribing FGAs.

    - to educate clinicians on how both FGAs and SGAs can be used effectively for specific patient populations.

- There is potential to expand effective and appropriate use of FGAs in specific patient populations rather than for widespread use in schizophrenia. The panel suggested exploring decision-making on an individual patient level, to deliver effective personalised antipsychotic therapy. Educational initiatives could include patient profiles.

- Each decision should be based on three factors: data, clinician experiences, and patient preferences.

What is the current role of FGAs?

This report summarises discussions that took place at the advisory board meeting held in Paris on 27 March 2023. The information herein reflects the personal views and experiences of the advisors who were present and may not reflect the opinions and experiences of others.

Setting	Patients	Examples	Country-specific information	Other
Emergency room/ acute units	Hospitalised and non-compliant schizophrenia	Haloperidol Clozapine	• Intramuscular (IM) formulations not popular in France/ Italy	• Long-lasting IM formulations are preferred to overcome non-compliance
	Severe agitation in schizophrenia	Haloperidol Levomepromazine Zuclopenthixol Chlorpromazine Cyamemazine Loxapine Tiapride/ pipamperone	• Cyamemazine available only in France • Loxapine use increasing in France • Chlorpromazine not used in Germany • Levomepromazine often used in drops • Pipamperone is used instead of tiapride in Germany	• Tiapride is used if alcohol consumption is suspected
Geriatric care	Cognitive/ behavioural disturbances in dementia	Low-dose haloperidol Any FGA available as drops		
Any	Treatment-resistant schizophrenia	SGA combinations with: Haloperidol Chlorpromazine Amisulpride	• Intravenous (IV) formulations not available in Germany/Italy	• Long-lasting IM formulations are often given in combination with the first-line SGA
Off-label use in primary care	General sedative for anxiety, stress, burnout, insomnia	Flupentixol IM Quetiapine Melperone Pipamperone Sulpiride Haloperidol (1–2mg)		• Sulpiride use varies widely between countries, in the extent of use and purpose

Table 1. Advisor's experiences of how FGAs are used in clinical practice around Europe.

Table 1 shows a summary of information gathered from a panel of European experts in psychiatry, regarding use of FGAs in current clinical practice. More country-specific detail can be found in the commentary below.

FGA use in Germany

There is little knowledge about FGAs among younger healthcare professionals (HCPs) in Germany. Experienced clinicians do use FGAs in specific (or 'niche') settings:

- Hospitalised non-compliant patients: FGAs may be administered as an IM injection or orally as tablets or fluid. In the large hospital network in which Prof. Hajak practises, all emergency wards use FGAs.
- Dementia: Low-dose haloperidol is used to improve cognitive and behavioural changes.
- ADHD and behavioural disturbances related to personality disorders: FGAs are used but infrequently.
- Treatment-resistant schizophrenia: FGAs are given as combination therapy for patients who do not respond to initial treatment. This is a last attempt to stimulate a response to treatment (often with flupentixol as long-acting IM injection).

GPs also use low-potency FGAs off-label. Examples include the following:

- weekly IM flupentixol for general anxiety.
- treatment of insomnia with pipamperone.
- melperone (an SGA that is structurally similar to haloperidol) prescribed to sedate people with non-specific conditions, e.g., stress, burnout.
- promethazine (an antihistamine) is used to treat further general conditions that require sedative properties, e.g., insomnia, anxiety.

The German national guidelines provide recommendations on the diagnosis and treatment of schizophrenia. The document provides general guidance on treatments, and recommends that decisions are made based on individual risk/benefit ratios. There is no clear definition of when to use FGA and SGA classes, giving clinicians freedom to choose the best treatment for each patient. However, SGAs are used more frequently than FGAs.

FGA use in Spain

Guidelines recommend antipsychotics but rarely recommend specific drugs. SGAs or both FGAs and SGAs are recommended for first-episode psychosis.

FGAs are mostly used in emergency settings and acute units to treat agitated patients:

- Haloperidol is the preferred FGA, as it is considered a good option for patients who may have consumed alcohol.
- Levomepromazine is used for highly agitated patients because of its sedative effects.
- Long-acting formulations are used for patients with low adherence, e.g., difficulties attending appointments.
- Zuclopenthixol is available in every hospital and is also used.
- FGAs are not used for other conditions like personality disorders or Asperger's syndrome.
- Dementia: FGAs are used for patients with delirium, because they are easy to administer as drops.
- Treatment-resistant schizophrenia: clozapine may be combined with an FGA to improve positive symptoms.
- Perphenazine is now used only for patients who are stable, for whom doctors do not want to change the patient's medication. FGAs are used for stable patients; IM flupentixol or zuclopenthixol can be used and if effective the patient continues therapy.

FGA use in Italy

Guidelines position SGAs for first-line therapy and FGAs as second-line therapy for schizophrenia. FGAs account for around 30% of antipsychotic prescriptions for schizophrenia in Italy. Younger HCPs have little experience with FGAs except haloperidol or zuclopenthixol, which are used in acute situations similar to those already described for other countries:

- Second-line therapy for schizophrenia: treatment typically starts with an SGA and then an FGA is added if there is resistance or loss of response.
- FGAs are used in severe situations in the emergency room (ER), e.g., in cases of delirium. Haloperidol IV is not available. Haloperidol is used if IV administration is not required.
- Dementia: FGAs are used to treat patients with severe behavioural disorders.
- Young patients with neurodevelopmental disorders: chlorpromazine is still considered the best option for treating agitation and is frequently used in severe cases.

FGA use in France

In France there is a clearer distinction in recommended use of SGAs and FGAs. The national guidelines (from the High Authority of Health, updated in 2018) recommend SGAs for first-line treatment of schizophrenia. FGAs are recommended only in later lines of therapy because of the associated risk of EPS.

FGAs are used in high doses in France, which may underlie the high risk of EPS. National guidelines note that SGAs are associated with metabolic complications, and monitoring is recommended. Unfortunately, monitoring is rarely undertaken in the real world, and metabolic syndrome is frequently observed among patients with schizophrenia.

A recent study of a French national database showed that around 20% of prescriptions for schizophrenia are for monotherapy with an FGA or SGA, and around 40% are for FGA/SGA combination therapy. A recent unpublished study in 400,000 patients has shown that the most frequently prescribed FGAs in France are haloperidol, cyamemazine and tiapride.

There are cultural aspects to how these drugs are used and perceived. Fluphenazine was used in France at a high dose (300 mg/day), whereas in the US, it was used at 10–20 mg/day. This example highlights how FGAs are used differently and how using high doses may have contributed to the perceived high risk of side effects with FGAs.

FGAs are used in niche settings:

- Haloperidol is the most prescribed FGA in France. Cyamemazine comprises around 20% of FGA prescriptions and is not currently available outside of France. It is prescribed over a large dose range: at low doses, it has an anxiolytic effect; at high doses, it has a sedative effect; and at very high doses (200 mg), it can be used in an injectable form to treat symptoms of agitation. However, there is no robust evidence for significant efficacy on psychotic symptoms, and cyamemazine is used for anxiety, agitation and sleep disorders.
- Tiapride is often used to treat alcoholism.
- Loxapine is increasingly used to reduce agitation in the ER setting.
- Non-adherent schizophrenia: patients may be treated with a long-acting injectable FGA, commonly haloperidol, sometimes in combination with clozapine.
- FGAs are also prescribed to treat behavioural disturbance in dementia, personality disorders, and adolescents with personality disorders (although supporting evidence is of poor quality).

What antipsychotic combinations are used in schizophrenia (and why)?

Since first-line therapy is typically with SGAs, FGAs are used as combination therapy in second-line and beyond. Addition of this second agent is often preferable to increasing the dose of first-line treatment, which carries an increased risk of side effects.

FGA combinations usually involve adding a long-acting injectable FGA, like haloperidol or flupentixol, to the SGA. In some cases, haloperidol is not used with clozapine because it reduces the effect of clozapine. Clozapine with amisulpride is preferred because the two components have different modes of action.

Combinations are also used to reduce agitation in severe schizophrenia and mania. Haloperidol (and, in some countries, pipamperone) is useful in treating bipolar disorder, hypomania, mania, agitation due to depression, etc.

Use of chlorpromazine varies between countries; it is not used in Germany, but in Spain and Italy, it can be used to treat severe neurodevelopmental disorders and agitation. In Italy, very high doses can be used (50–300 mg). It is used in the ER because it is fast-acting.

In which patients would you NOT use FGAs?

- Patients suffering from schizophrenia who are adherent and willing to take their medications. A favourable risk/benefit ratio means SGAs are generally more suitable for these patients.
- Any patient developing EPS. FGA treatment is stopped at once to prevent further long-term complications.
- First-episode psychosis.
- Any patient at risk of developing depression or EPS, e.g., schizoaffective disorder or Parkinson's disease. Patients at risk of depression should not receive haloperidol but could be considered for other non-depressive FGAs such as perphenazine.

Dyskinesia

Fear of this long-term irreversible symptom is a barrier to FGA use for some psychiatrists in Spain and Germany. In France and Italy, the focus is on immediate rather than long-term risks, so dyskinesia is not a barrier. This side effect can also occur with SGA therapy, especially in individuals over 65 years of age.

Negative symptoms

There is a lack of good therapeutic options to treat the negative aspects of schizophrenia. France considers sulpiride/alizapride useful for negative symptoms at low doses.

Are all FGAs alike? What criteria do you use to distinguish them?

Antipsychotics may be subclassified beyond FGA/SGA, often described based on their effects, i.e., anti-agitation/sedative, antipsychotic, and (in some countries) sleep-promoting. Such differentiation is considered only by older doctors; younger doctors simply disregard FGAs because of side effects.

The advisors noted psychopharmacology manuals or reference books used in each country to guide the appropriate use of antipsychotics. However, experience provides better guidance than the 'recipes' in these books. Experience will tell, for example, how different effects can arise from different doses of the same drug.

Have FGAs fallen into specific 'niches', or are they being used to the full extent of their indications? If not, why?

Advisors agreed that FGAs are used in specific niche patient populations across Europe, largely driven by empirical knowledge from experienced clinicians. Lack of education means younger doctors have little knowledge about FGAs, and safety fears prevent these from being prescribed. There is potential to expand FGA use within these niche indications rather than as a widespread treatment for schizophrenia.

CHLORPROMAZINE

This FGA is not used in Germany following a 'red hand warning' from the German government. In Spain, Italy and France, chlorpromazine is used for sedative purposes in agitated patients and patients with mania, neurodevelopmental disorders, etc.

SULPIRIDE

Use of sulpiride is not widespread and where it is prescribed, it is mostly by GPs. In Spain, it is prescribed for dizziness, and in France, for non-specific pain. It is also used at low doses

(50–100 mg) for anxiety/depressive symptoms in France. In Italy, sulpiride has been replaced by other drugs, e.g., amisulpride.

LEVOMEPROMAZINE

This FGA is used for its sedative and sleep-inducing properties. Drops and injectable formulations are easy to administer to agitated patients and are used in emergency settings in Spain and Germany. Drops are not available in Italy and so it is administered in pill form. In France, cyamemazine is often used in place of levomepromazine, administered as drops and pills.

PERICIAZINE

None of the advisors reported experience of using this FGA.

TIAPRIDE

This FGA is not used in Spain. In Germany, it is used in patients with alcoholism and its use could be expanded in this indication. Pipamperone is often used instead of tiapride.

In Italy, tiapride is used in the IV formulation for delirium tremors, and in Tourette's syndrome (tiapride is not depressionogenic, unlike other FGAs). It was also used during the COVID pandemic in the emergency setting. It is described as selective and effective, and is available in an IV formulation. Its use to treat neuroleptic disorders was also mentioned. In France, use of tiapride for alcohol withdrawal or delirium has declined following a change to the licensed indication around 8 years ago.

PIPAMPERONE

This FGA is not used in France. In Italy and Germany, it is used for its sedative rather than antipsychotic properties, e.g., for patients with bipolar disorder who are prone to developing depressive symptoms. Some advisors prefer it to SGAs because there is no associated risk of weight gain.

ZUCLOPENTHIXOL

This FGA is not used in France. Use of the IM formulation is increasing in Germany, where its long-lasting effects are considered beneficial in some settings.

Advisors anecdotally described situations in which patients treated with an SGA gain weight are consequently switched to a different SGA; this approach can result in poor efficacy. There is an opportunity to switch these patients to FGAs to avoid weight gain and retain efficacy.

The robust efficacy of FGAs on core psychotic symptoms in specific patients could be highlighted and anchored in guidelines.

How do FGAs compare with SGAs?

The advisors agreed that these two types of antipsychotics are used for different purposes and should not be compared. Decision-making should be based on the comparison of individual drugs rather than on whether they are classified as FGAs or SGAs.

In addition, it is important to bear in mind the way data on antipsychotics have been collected in clinical trials. The general perception is that SGAs have a better safety profile than FGAs, but if one looks more closely, the methodologies used to compare FGAs and SGAs may have produced an unfair picture. While the current focus is on the safety profile of FGAs, there is potential to explore the fact that FGAs have better efficacy in acute settings when a patient's need is greatest.

Trial populations

Patients in clinical trials typically have less severe schizophrenia than patients seen in acute settings where FGAs are used in the real world. High doses of FGAs are used to stimulate efficacy in the trial populations, and the effects are compared with relatively low doses of SGAs. Of course, FGAs exhibit more side effects in such comparisons than the low-dose SGAs. Other evidence indicates a high receptor occupancy at lower FGAs doses (e.g., haloperidol 6 mg), and the use of such lower doses could be explored further as a way of reducing side effects of FGAs.

Use outside of schizophrenia

Low-dose FGAs are currently used as sedatives to treat a mixed population of patients diagnosed with early stages of depression, anxiety, etc. Such indications outside of schizophrenia could be explored further since low doses are needed and the risk of EPS should be less of a barrier to FGA use.

Duration of onset of side effects

While EPS typically appears quickly upon treatment with FGAs, the metabolic side effects associated with SGAs may take many months or years to develop. EPS is, therefore, a more immediate concern for prescribers than metabolic side effects. However, the high prevalence of metabolic syndrome among patients taking antipsychotics indicates a major impact on long-term patient health and quality of life. Advisors described patients gaining >10 kg per year when treated with SGAs, and they reported a high prevalence of metabolic syndrome and obesity.

Duration of treatment

Side effects like EPS and dyskinesia are observed more frequently in the real world than with SGAs. However, patients receiving FGAs have often experienced loss of response to first-line SGA treatment and have been treated for long periods of time. Therefore, multiple factors throughout the patient journey may be contributing to these patients' susceptibility to EPS and dyskinesia.

Metabolic complications

Currently, the distinctions between FGAs and SGAs are too simplistic. FGAs are better in emergency settings because they produce a reliable, strong effect, but this is associated with higher risk of EPS. FGAs are less well tolerated when used in long-term treatment; advantages of a treatment in one situation can be seen as disadvantages in another.

The patient's opinion should also play a role in decision-making. Young people are particularly concerned about gaining weight or suffering negative symptoms associated with SGAs. Patients who already have metabolic issues like diabetes are not suitable for treatment with olanzapine, for example. More details are needed about the metabolic effects of individual drugs to inform decision-making.

Some guidelines do highlight the need for monitoring patients for metabolic syndrome. They rank compounds according to metabolic risk, with olanzapine and clozapine having the highest risk. Despite specific guideline recommendations in France, metabolic side effects remain problematic: an ongoing study shows that 30% of patients with schizophrenia have metabolic syndrome, and around 75% of these patients go untreated for this condition.

Education strategies for HCPs regarding FGAs

All advisors agreed on the need for more education for young clinicians on the appropriate uses of FGAs and SGAs, especially regarding niche indications in which FGAs can be used effectively. Clinicians should be more aware of the nature of comparisons made between different antipsychotics, and the situations in which different doses can be used appropriately to achieve the right effects without fear of side effects. Some evidence supports that FGAs could be used as first-line therapy.

There are opportunities to expand FGA use in other indications, such as in elderly populations with behavioural disturbance and sleep disorders. In Germany, patients with dementia in nursing homes often receive antipsychotics, but only risperidone is approved within this indication. Other drugs are prescribed off-label, and more options within the approved label are needed. New formulations like risperidone ISM® are bringing attention back to FGAs and 'older' drugs, encouraging younger clinicians to use them.

The current trend towards structured treatment algorithms and individualised decision-making could be applied to FGAs. Appropriate drugs would be chosen on a per-patient basis, considering factors like whether the patient is obese, aggressive, etc. However, a question was raised over whether such a decision algorithm could be based on opinions and experiences rather than data. There is a belief that knowledge and decision-making should not be restricted to data collected in clinical trial populations – this approach is not realistic, especially in schizophrenia.

In summary, case-centred education, alongside other approaches, may be useful to fill a large knowledge gap currently surrounding the use of antipsychotics.

