Neuropsychiatric Disease and Treatment

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EXPERT OPINION

On the Road to Individualizing Pharmacotherapy for Adolescents and Adults with Schizophrenia – Results from an Expert Consensus Following the Delphi Method

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Introduction: Schizophrenia is a severe mental illness that usually begins in late adolescence or early adulthood. Current pharmacological treatments, while acceptably effective for many patients, are rarely clinically tailored or individualized. The lack of sufficient etiopathological knowledge of the disease, together with overall comparable effect sizes for efficacy between available antipsychotics and the absence of clinically actionable biomarkers, has hindered the advance of individualized medicine in the treatment of schizophrenia. Nevertheless, some degree of stratification based on clinical markers could guide treatment choices and help clinicians move toward individualized psychiatry. To this end, a panel of experts met to formally discuss the current approach to individualized treatment in schizophrenia and to define how treatment individualization could help improve clinical outcomes.

Methods: A task force of seven experts iteratively developed, evaluated, and refined questionnaire items, which were then evaluated using the Delphi method. Descriptive statistics were used to summarize and rank expert responses. Expert discussion, informed by the results of a scoping review on personalizing the pharmacologic treatment of adults and adolescents with schizophrenia, ultimately generated recommendations to guide individualized pharmacologic treatment in this population.

Results: There was substantial agreement among the expert group members, resulting in the following recommendations: 1) individualization of treatment requires consideration of the patient's diagnosis, clinical presentation, comorbidities, previous treatment response, drug tolerability, adherence patterns, and social factors; 2) patient preferences should be considered in a shared decision-making approach; 3) identified barriers to personalized care that need to be overcome include the lack of actionable biomarkers and mechanistic similarities between available treatments, but digital tools should be increasingly used to enhance individualized treatment.

Conclusion: Individualized care can help provide effective, tailored treatments based on an individual's clinical characteristics, disease trajectory, family and social environment, and goals and preferences.

Keywords: psychosis, psychopharmacology, treatment, personalized, psychiatry

Received: 22 December 2023
Accepted: 27 April 2024
Published: 24 May 2024

Introduction

Schizophrenia is a mental disorder characterized by a persistent tendency to recurrent psychotic symptoms associated with cognitive, emotional, behavioral, psychological, and social dysfunction,[1] generally characterized by a fluctuating clinical course with relapses and remissions.[2–6] Schizophrenia affects approximately 7/1000 people, with a male-to-female ratio of approximately 1.4:1[4,7,8] and causes a significant clinical, personal, and economic burden,[9–11] with patients continuing to experience impairment in activities of daily living, work capacity, and social functioning.[12–14]

While psychopharmacology remains the cornerstone of schizophrenia treatment,[15–20] the addition of psychosocial interventions or psychotherapy is essential to improve the overall personal and family well-being of individuals affected by this complex mental disorder.[21,22] The ability to improve outcomes across multiple relevant domains may be further enhanced when psychosocial and psychotherapeutic interventions are integrated into an Early Intervention Services (EIS) framework for people with early-onset psychotic disorders.[23] A recent umbrella review found several psychosocial and psychotherapeutic interventions to be superior to usual care in high and moderate quality meta-analyses. These included EIS and cognitive behavioral therapy (CBT) for the primary outcome of total symptom improvement. For 14 secondary outcomes, EIS was also superior to usual care, except for cognition, highlighting the importance of early comprehensive treatment approaches in the early stages of schizophrenia spectrum disorders. In people with established schizophrenia, mixed family interventions were effective for positive symptoms, negative symptoms, and quality of life (QoL); CBT for positive and negative symptoms, relapse prevention, functioning, and QoL; psychoeducation for relapse prevention; cognitive remediation therapy for cognition and functioning; and hallucination-focused integrative treatment for positive symptoms.[21] In addition, a recent network meta-analysis of psychological and psychosocial interventions for relapse prevention in schizophrenia found that family interventions, patient and family psychoeducation, CBT, integrated interventions, and relapse prevention programs were superior to usual care in preventing relapse at 12 months.[22] While it remains a challenge to disentangle whether the relapse prevention effect may be mediated by other factors, such as direct family involvement and/or improved adherence to psychopharmacological treatment, psychotherapy and psychosocial interventions may enhance the established relapse prevention efficacy of antipsychotics, particularly long-acting injectable antipsychotics,[24] in people with schizophrenia.

Supported employment and training programs can further contribute to the rehabilitation of people with schizophrenia by promoting vocational skills and facilitating medium- to long-term community integration.[25,26]

The concept of "precision medicine" was widely popularized around the Precision Medicine Initiative launched by the Obama administration in 2015.[27] However, the term had been used before, initially limited to some areas of oncology, at a time when classic prognostic tools such as tumor size, extension, and stage were beginning to be supplemented by some gene expression variables with relevance to treatment outcomes.[28] This terminology rapidly spread to other areas of medicine, including psychiatry,[29] where the term "personalized" seemed to gain more traction. In general, "precision medicine" takes into account broader differences in people's genes, environments, and lifestyles to design specific prevention and treatment strategies that may be effective for some but not for all individuals, abandoning the traditional one-size-fits-all approach.[30] Personalized medicine, however, also takes into account demographic and disease characteristics, and past, current, or future treatment effects, as well as patient goals and preferences, with the aim of optimizing care and improving outcomes for each individual.To further complicate an already confusing collection of terms, the term "individualized medicine" is also used in this context. While "personalized medicine" and "individualized medicine" are often used interchangeably, they may have slightly different connotations depending on the context. In our view, and for the purposes of this paper, personalized medicine, although tailored to the individual, often emphasizes the role of molecular and genetic information in tailoring treatments, whereas individualized medicine would include a more comprehensive view of an individual's clinical and health profile, as well as his or her goals and preferences. The larger field of "precision psychiatry", including genetics and other biomarkers, is beyond the scope of this paper. Nevertheless, such measurable indicators of underlying biological processes or states have the potential to improve diagnostic accuracy, predict treatment response, and deepen understanding of the underlying neurobiological mechanisms associated with the disorder. Therefore, augmenting the field of psychiatry, which relies mostly on self-reports, informant reports, interviews and behavioral observation, by linking these data points to biological assessments[31–38] is an aspirational goal that needs to be pursued further. However, while some genetic, immunological, clinical, and neuroimaging biomarkers have shown potential, particularly in the areas of predicting conversion to psychosis and treatment response, discontinuation, and relapse risk, no single biomarker has been able to achieve disease- or

practice-modifying impact despite extensive research over decades.[5,39–41] Nevertheless, the lack of actionable biomarkers should not lead to the conclusion that individualized management of schizophrenia is not feasible.

In clinical practice, patients vary widely in their response to treatment, which is consistent with data showing that schizophrenia is highly heterogeneous in terms of clinical manifestations, treatment response, and outcomes.[42–44] Interestingly, a recent meta-analysis of 52 randomized controlled trials in adults with a diagnosis of schizophrenia or schizoaffective disorder, designed to assess whether patients vary in their response to antipsychotics, found no personal element to treatment response, with less variance in treatment than in the placebo group,[45] suggesting that there is little room for individualized treatment and that efforts to develop such treatment strategies for schizophrenia may be misguided. Although the methodology of this study was sound, these results appear to be at odds with clinical practice. One possible explanation for these discrepancies may be due to generalizability issues, as patients enrolled in blinded, randomized, placebo-controlled clinical trials are highly selected and represent only about 20% of the general schizophrenia population.[46] Other explanations may involve methodological issues. For example, a recent study using individual patient data and study-level data (rather than averages) to quantitatively characterize the heterogeneity of antipsychotic treatment effects in schizophrenia showed, in contrast to the previous study, marked variability in antipsychotic-specific effects among individuals with schizophrenia, with the top quartile of patients experiencing beneficial treatment effects of 17.7 points or more on the Positive And Negative Syndrome Scale (PANSS) total score,[47] suggesting that treatment response may be very much related to individual factors for each specific patient.

Given all of the above, the overall goal of this project was to review, discuss, and summarize the current state of treatment individualization for adult and adolescent patients with schizophrenia and to provide some expert recommendations on how treatment individualization can help improve clinical outcomes.

Materials and Methods

An expert group of seven experienced academics and clinicians with relevant expertise in the field of psychosis in both adult and adolescent populations met during the 36th Congress of the European College of Neuropsychopharmacology, which was held in Barcelona in October 2023. Prior to the meeting, participating experts were sent a link and invited to complete a questionnaire about individualized treatment of people with schizophrenia and rate their level of agreement or disagreement with each item on a 9-point Likert scale (0=strongly disagree, 9=strongly agree), following a previously described Delphi approach. Briefly, the Delphi method is a structured research procedure that repeatedly and anonymously polls a panel of experts, allowing participants to modify their responses during each successive round that focuses on areas where consent is lacking or additional information needed to be provide to provide further grounds for the consensus process, until a consensus about a given topic is reached.[48–50] In addition, a comprehensive and critical review of published scientific literature relevant to the individualized treatment of people with schizophrenia was conducted and made available during the meeting to inform discussions. During this meeting, participants discussed and synthesized recommendations for the individualized treatment of patients with psychotic disorders, shared their research and clinical experiences, and offered suggestions for advancing knowledge in the field and improving clinical care focused on the individualized treatment of people with schizophrenia. For statements and items for which consensus was not reached in the first round of ratings conducted prior to the meeting, or for which clarification was needed, these items were discussed during the meeting and panelists were asked to re-rate these items electronically in a second round, and so on, until consensus was reached. Descriptive statistics were used to average and rank the individual items based on the expert responses, which are summarized in the Results section of this manuscript. This manuscript integrates information from individual expert presentations, collective discussions, responses, comments, and feedback from all panel members, along with a review of the evidence. Due to the nature of the manuscript that does not contain any patient-related data or study subjects, no review and approval by an institutional review board or ethics committee is required.

Results

The panel agreed that general factors to consider when implementing treatment individualization include taking into account the patient's diagnosis, comorbidities, previous treatment response and tolerability, adherence patterns, and patient preferences. On this last point, it is always recommended to emphasize a respectful and humane approach, framed

by shared decision making and motivational interviewing approaches. Nevertheless, the expert panel was roughly divided when asked whether personalized treatment for schizophrenia is currently possible. Barriers cited included the lack of readily available clinical or biological markers, as well as mechanistic similarities between treatments that prevent the desired sophisticated stratification or personalization of care. In addition, lack of time or paternalistic approaches to care can hinder the individualization of care by reducing the focus on patient preferences and choices.

Beyond these general principles, however, some recommendations have been made based on clinical stratification variables. A detailed summary of the recommendations is provided in Table 1. For example, in patients with predominant negative symptoms, medications that produce sedation and extrapyramidal symptoms should be discouraged because they may themselves produce secondary negative symptoms.[51,52] Although no pharmacologic treatment is approved for negative symptoms, low-dose amisulpride and cariprazine[53] or the addition of antidepressants in people with negative symptoms secondary to depression or in people without depression but with negative symptoms that are resistant to antipsychotics could be considered.[54–56] For patients with predominant cognitive symptoms, although there appear to be no clear differences among antipsychotics,[57] avoidance of sedating medications, especially those with strong anticholinergic properties, is recommended.[58] In addition, because of the association between cognitive symptoms and cardiometabolic risk, medications with an adverse metabolic profile should also be avoided.[59] In addition, the panel agreed that cognition is a relevant outcome target for which there is currently no indicated treatment, but that clinicians should at least make a treatment choice that does not worsen cognition, including not using anticholinergic medications to mask extrapyramidal side effects. Importantly, prolactin-raising antipsychotics should be used with caution in women.

A recent nested case-control study using nationwide health record data showed that long-term exposure to prolactin-increasing, but not prolactin-sparing, antipsychotics was associated with an increased risk of breast cancer.[60] Finally, people with psychosis suffer from increased morbidity and mortality related to physical comorbidities, particularly cardiometabolic disease, resulting in a significantly reduced life expectancy.[61,62] This has been attributed in part to the cardiometabolic side effects of antipsychotics, but unhealthy lifestyle behaviors also contribute to the risk. This has been attributed in part to the cardiometabolic side effects of antipsychotic medications, but unhealthy lifestyle behaviors also contribute to risk.[63,64] However, continued antipsychotic treatment has actually been shown to reduce all-cause and specific-cause mortality from both unnatural causes (mainly suicide) and natural causes (mainly cardiovascular disease),[61,65] in part because of healthier lifestyle behaviors and better adherence to secondary preventive treatments such as antidiabetic, statin, and antihypertensive medications.[66]

Therefore, the panel recommended that careful selection of antipsychotic medications, close monitoring of metabolic and weight gain variables, coupled with promotion of a healthy lifestyle, are necessary for successful treatment. Overall, the individualization of treatment is seen as a very dynamic process, because many (but not all) of the factors described above are mutable, and while some side effects may be considered undesirable for a given individual at a given time (eg, increased appetite), they may be good for the same patient at another time in the course of the illness, or for other patients.

The panel was asked what factors are considered most important when tailoring an individualized treatment plan for schizophrenia in a newly diagnosed patient and a previously treated patient. The top five factors for each category are listed in Table 2. Lower ranked factors included biomarkers, genetic factors, and cost of treatment in both groups.

Factors that the panel felt influenced discontinuation and non-adherence were also discussed. Among the experts, the results were similar for both scenarios, with limited awareness/illness recognition and medication side effects topping both lists with a median score of 9.0, followed by oral/long-acting formulation for discontinuation and drug use (median: 8.0) and for non-adherence (median: 8.0). The experts also ranked which of the PANSS dimensions influenced their decision-making regarding antipsychotic treatment choice, with positive symptoms ranking highest and anxiety/depression ranking lowest. The panel was also asked which factors they thought had the greatest impact on the level of functioning of a person with schizophrenia, with cognitive and negative symptoms ranking highest and genetic and biological factors ranking lowest.

As noted above, individualized treatment also involves making treatment choices based on the adverse event profile. To this end, experts ranked concerns about adverse effects, both short-term and long-term. Highly ranked items are shown in Table 3. Briefly, neuroleptic malignant syndrome and neutropenia/agranulocytosis were ranked highest as short-term concerns (median: 9.0), whereas various cardiovascular and metabolic side effects and neutropenia/agranulocytosis were ranked highest as long-term concerns.

Table 1 Important Elements/Variables to Consider for Successful Individualized Treatment

Element/Variable	Key Treatment Considerations
Immutable	
Age	Younger patients may be more sensitive to antidopaminergic side effects, require lower starting antipsychotic doses, slower titration, and possibly lower maximum doses. In addition, early-onset schizophrenia is associated with poorer adherence, and with greater treatment resistance. Older patients are more susceptible to side effects, require caution due to more physical comorbidities, and generally require lower antipsychotic doses.
Sex	Caution is warranted with prolactin-raising antipsychotics, possibly increasing the risk of breast cancer. Consider individual differences in side effect-associated discomfort (eg, sexual dysfunction) and impact on treatment.
Mutable	
Positive symptom severity	More sedative medication may be needed temporarily in an acute setting, for acute agitation or aggression. Given overall equivalent efficacy, focus on tolerability and patient preference, thinking of the long-term is encouraged. Monitor response and treatment resistance. Consider clozapine early.
Negative symptoms severity	Monitor and treat the cause of secondary adverse symptoms. Avoid sedating and EPS-producing drugs or doses. Consider low-dose amisulpride or cariprazine for primary negative symptoms. Consider antidepressant augmentation and non-pharmacological interventions.
Cognitive symptom severity	Monitor and treat the cause of secondary cognitive symptoms. Avoid sedating and EPS-producing medications or doses, avoid medications with relevant anticholinergic properties. Mind cardiovascular side effects. Consider non-pharmacological interventions.
Affective symptom severity	More sedating medications may be needed temporarily for manic/agitated episodes or those with severe insomnia, but a switch to non-sedating, non-weight gain-producing antipsychotics should occur soon, or non-sedating antipsychotics may be temporarily paired with sedating medications (benzodiazepines, sedating antipsychotic, or antidepressant). Adjunctive antidepressants may be needed for depressive episodes.
Insomnia	Various therapeutic options should be considered, including night-time dosing. Consider especially non-pharmacological strategies. Benzodiazepines may be considered in the short term, but Z-drugs are preferable.
Family or personal history of treatment response	Consider using treatments with patient or family history of previous response and adequate tolerability. Avoid unnecessary retrials, unless reasonable doubts about adherence or adequate dosing exist.
Social support and stigma	Stigma and self-stigma affect treatment acceptance and adherence and can have different impact in different subgroups or at different illness stages (eg, social media input may affect younger patients more than older patients). Patient and family psychoeducation is fundamental. Long-acting injectable (LAI) antipsychotics should be considered overall, but particularly in case of low social support/homelessness.
Patient preference and adherence patterns	Always consider patient's preference to enhance therapeutic alliance and hopefully adherence. When non-adherence is suspected, do not delay proposing long-acting injectable medication.
Presence of comorbidities (physical health)	Mind pharmacological interactions. Avoid treatments with poor metabolic side effect profile. Focus on non-pharmacological, lifestyle interventions including diet, physical exercise, and smoking cessation.
Presence of substance abuse and type of substance	Requires additional, specific, specialized treatment approaches. Consider avoiding high-potency dopamine blockade. Consider long-acting injectables due to sustained blood levels and risk of nonadherence associated with drug use. Be aware of relapse and increased risk of treatment resistance.

When asked which side effects they thought their patients were most concerned about, dystonia topped the list, followed by anticholinergic effects, weight gain, prolactin elevation/sexual side effects, and sedation/somnolence, with all four tied.

Table 2 Top 5 factors to consider for an individualized treatment plan for schizophrenia in a newly diagnosed patient and a previously treated patient.

First-Episode Patients		Previously-Treated Patients	
Score (Median)	**Item**	**Score (Median)**	**Item**
9.0	Type of Symptoms	9.0	Severity of Symptoms
9.0	Severity of Symptoms	9.0	Drug Safety
9.0	Physical Comorbidities	9.0	Prior Treatment Response to Specific Medications
9.0	Patient Preference	9.0	Prior Side Effect to Specific Medications
8.0	Drug Tolerability Profile	9.0	Patient Preference

Table 3 Top 5 concerns about treatment adverse effects, both short-term and long-term.

Short-Term Concern		Long-Term Concern	
Score (Median)	**Adverse Effect**	**Score (Median)**	**Adverse Effect**
9.0	Neuroleptic malignant syndrome	9.0	Glucose metabolism/diabetes
9.0	Neutropenia/agranulocytosis	9.0	Weight gain
8.0	Anticholinergic effects	9.0	Dyslipidemia
8.0	Agitation	9.0	Neutropenia/agranulocytosis
8.0	QT prolongation	8.0	QT prolongation

Finally, the experts were asked for general recommendations when a patient decides not to take or to discontinue medication against medical advice. The panel agreed that if a patient is in acute danger to themselves or others, immediate action is warranted. Recommended actions for patients who are not in danger to themselves or others and who decide to discontinue (or not take) medication are listed in Table 4.

Table 4 Recommended Actions When a Patient (Who is Not in Danger to Themselves or Others) Decides to Stop Medication, Ordered by Relevance/ Score, from Top to Bottom

Expert Recommended Actions
Review risk/benefits and alternatives
Recommend slow discontinuation
Develop a crisis plan/advanced directives
Patient - education about early signs of relapse
Maintain firm yet supportive attitude/stand
Intensify monitoring
Family/Caregiver – education about early signs of relapse
Increase therapeutic support
Increase non-therapeutic/social support

Discussion

While the long-awaited precision psychiatry remains elusive, identifying clinically meaningful groups of individuals with potentially different profiles that can guide the selection of specific treatments based on patient and medication characteristics is an immediate priority.

When the panel was asked about the factors primarily considered when tailoring an individualized treatment plan for a newly diagnosed patient with schizophrenia versus a previously diagnosed and treated patient, previous treatment experience, both in terms of efficacy and side effects, was highlighted in the case of previously treated patients. Interestingly, in both cases there was a dissociation between the functional impact of symptoms, which was not rated highly, and symptom severity and type, which were rated highly, probably because, unlike symptom severity, treatment does not seem to affect global functioning as much, or because global functioning is strongly determined by symptom severity and type. Beyond the secondary effects of improving schizophrenia symptoms, psychosocial and educational/vocational functioning are more likely to be improved by psychosocial and psychotherapeutic interventions. Drug mechanism also ranked high, although the efficacy of antipsychotics was comparable across meta-analyses, probably due to the different mechanisms that influence the likelihood and severity of side effects.[67] Not surprisingly, biomarkers and genetic factors ranked lowest, probably due to the lack of direct, actionable effects in modulating treatment choice.

Factors that might influence discontinuation and non-adherence were also discussed by the expert panel. Interestingly, age and gender were ranked relatively low, suggesting that the panel may have considered antipsychotic discontinuation to be a risk across all age and gender groups. However, a recent study in a national cohort of patients with first-episode psychosis showed that the younger the patient, the more likely they were to discontinue treatment, with the risk of discontinuation decreasing with successive episodes of treatment, and that the risk of discontinuation was lower for men than for women with schizophrenia (aHR = 0.83 vs women; 95% CI = 0.77–0.88).[68]

Typically, schizophrenia is diagnosed in the second or third decade of life, although according to a recent meta-analysis, 2% of cases may occur before the age of fourteen and 12% before the age of eighteen.[69] However, up to 50% of cases may occur before the age of 25.[69] Beyond the specific case of children, where certain medications need to be prescribed off-label, the Expert Group agreed that age should be considered as a continuous factor, as it is one of the variables/contributors that, together with other clinical variables (severity of illness, comorbid substance use, etc.), will help guide the choice of treatment, particularly in relation to preferences for adverse effect risk, as younger patients and those who are treatment-naive are more sensitive to antipsychotic adverse effects.[70–72] However, there are some factors that need to be considered specifically for the adolescent population, as age is not a linear factor. Adolescence is a period of intense physiological, psychological and social change.[73] Developmental aspects, involvement of family and caregivers, social factors related to school, among others, are relevant aspects to consider when individualizing treatment for this specific population.

Unfortunately, the transition from child and adolescent services to adult services can pose a risk of dropout and hinder engagement.[74] The appropriate age for transition from child and adolescent to adult services should be flexible, allowing for the possibility of extending it to an older age if needed, for example, if the patient turns 18 during an acute phase of the disorder.[75] The individual patient's readiness should be assessed prior to initiating the transition process.[76,77] Other challenges include changes in legal capacity, where young adults begin to assume full responsibility and are expected to make important decisions about their own care, while parents may feel excluded from decisions and information about their child's mental health, which can be stressful for both.[75] A strong therapeutic alliance, shared decision-making, and a comprehensive, supportive, person-centered approach to care have been identified as the most important factors in sustained treatment engagement.[78] In summary, the goal for health care professionals working with patients with schizophrenia transitioning from adolescence to adulthood is to facilitate purposeful and stable patient participation in individualized, evidence-based, and age-appropriate treatments.

Experts were also asked to rank which of the PANSS dimensions influenced their antipsychotic medication, with positive symptoms ranking highest and anxiety/depression ranking lowest. Since anxiety and depression are generally not primary outcomes in the treatment of psychosis, it is not entirely surprising that these dimensions scored lower than positive symptoms. Interestingly, when asked what factors affect the level of functioning of a person with schizophrenia, genetic and biological factors scored the lowest, probably related to the lack of readily available biomarkers and the complex biological underpinnings of functioning. In contrast, cognitive and negative symptoms ranked higher than

positive symptoms, highlighting once again the apparent dissociation between symptomatic and functional outcomes and the fact that current antipsychotics treat positive symptoms better than negative and cognitive symptoms, which thus contribute significantly to residual functional impairment.[79–83]

Of note, recovery in patients with schizophrenia is defined not only by remission of positive and relevant negative symptoms that are no more than mild,[84] but also by functional performance in self-care, social interactions, leisure, and education/work.[85,86] In fact, fewer than 15% of patients with schizophrenia meet criteria for recovery, considering both clinical and functional status with persistence for at least 1 or 2 years.[12]

All of the above is further complicated by the fact that there is no clear and widely accepted consensus on the definition of relapse in schizophrenia, even though it is a very important outcome. Aiming to address this issue, a recent study analyzing data from seven RCTs (n=2354 adult participants with schizophrenia or schizoaffective disorder) showed that an increase of 12 points or more in PANSS total score corresponded to clinically significant worsening, equivalent to ≥1 point increase in CGI-S and ≥10 points decrease in functioning, measured with either the Personal and Social Performance Scale (PSP) or the Social and Occupational Functioning Assessment Scale (SOFAS), as opposed to the traditionally used percentage changes, the interpretation of which depends on baseline scores.[87]

Panelists also discussed how side-effect profiles can guide treatment choices. Recently, a number of patient- and prescriber-guided tools have been developed that take into account patient and treatment characteristics to formulate specific recommendations for specific patients to maximize efficacy while minimizing side effects and burden. Van Dijk et al[88] have developed an online treatment choice tool called the Personal Antipsychotic Choice (PAC) Index, currently available only in Dutch.[89] Using this tool, patients indicate on a 5-point Likert scale how they rate each side effect, which is combined in an algorithm with antipsychotic rankings to create a personalized ranking. Similarly, other recently developed tools allow patients to specify their individual weighting for a particular side effect and, based on such inputs, an algorithm shows which medications should be avoided.[90]

Another coordinated effort to create a comprehensive database of antipsychotic and antidepressant side effects has recently been undertaken, based on the results of an umbrella review of 68 meta-analyses of randomized controlled trials evaluating antipsychotic monotherapy in the treatment of schizophrenia or antidepressant monotherapy in the treatment of major depressive disorder[91]. For side effects for which data from randomized trials were not available, information was drawn from seven guidelines on antipsychotic and antidepressant side effects. In addition, a digital tool, the Psymatik Treatment Optimizer, was developed to assist in the clinical decision-making process involving the delicate balance between efficacy and side effects, facilitating database navigation while taking into account user and clinician concerns, and ranking 32 antipsychotics from best to worst after instantly calculating up to 11,618 pairwise drug/side effect comparisons in order of side effect preference for the individual user, with the output presented in the form of a heat map graph to inform clinical practice and improve outcomes.[91]

Another such tool to consider when choosing antipsychotic treatments for schizophrenia is the Shared Decision Making Assistant (SDMA),[92] which is available in multiple languages and includes data from existing network meta-analyses. The SDMA allows patients and clinicians to visualize interactive forest plots displaying data on the efficacy and side effects of different medications, which can be ranked. The clinical utility of SDMA is currently being evaluated in a randomized clinical trial.[93]

All of these tools do not provide recommendations for special situations, such as older age, renal or hepatic impairment, pregnancy, or lactation, probably because there is generally a lack of data on these populations to include in the algorithms. In addition, the number of antipsychotics included in each tool varies. Importantly, these tools are, at their core, individualized shared decision-making tools, a desirable approach in which patients and health care professionals make decisions about the patient's care together, based on open, evidence-based communication of information, discussion of pros and cons, and mutual agreement on treatment plans and desired outcomes.

In this context, the experts were asked about recommendations when a patient decides not to take or to discontinue a medication against medical advice. While this is a very complex issue with multiple overlapping layers that will not be discussed in depth here, the panel agreed that immediate action is warranted when a patient is in acute danger to themselves or others. Advance directives could mitigate some of the problems associated with this scenario. A recent meta-analysis aimed at determining the comparative effectiveness of interventions to reduce the rate of involuntary admissions among adult psychiatric patients (n=1102) found that advance directives were associated with a 23% risk

reduction (R=0.77; 95% CI: 0.60–0.98) in involuntary admissions, while other interventions, such as community treatment orders, integrated treatment, or compliance enhancement, were not.[94] A more recent multicenter randomized clinical trial showed that advance directives facilitated by peer workers were effective in reducing involuntary admission at 12 months (27.0% vs 39.9% in the control group (risk difference: −0.13; 95% CI, −0.22 to −0.04; P = 0.007).[95] However, the patient's capacity to understand and make decisions is fundamental to the validity and usefulness of advance directives, which may not always be predictable (eg, in a first psychotic episode). Overall, this panel believes that advanced directives have been shown to be effective in reducing involuntary admissions and can help promote patient autonomy and involvement in their own medical care plan, and should therefore be encouraged whenever possible.

As a new and evolving field, facilitated by technological advances and hampered by current imprecision, its application presents ethical challenges. These challenges have recently been reviewed and an action list of issues that need to be addressed from an ethical perspective in order to maximize the potential benefits of precision psychiatry has been developed.[96] The eight key priorities identified from this roadmap effort for the implementation of precision psychiatry in mental health include: 1) learning from somatic medicine, where precision medicine has already been successfully applied; 2) identifying and leveraging use cases for precision psychiatry; 3) increasing transparency and generalizability of the approach; 4) advancing implementation; 5) promoting mental health literacy; 6) communicating risk estimates in an understandable and balanced way; 7) ensuring data protection and privacy; and 8) fostering equitable distribution of mental health care. Academia, implementation science, appropriate service user involvement, and health care administration must all work together to facilitate the careful implementation of precision psychiatry, despite the still inadequate identification of predictive models and, in particular, their internal and external validation in mental health disorders.[97]

In this context, it is hoped that digital tools, ranging from passive sensing devices to interactive assessments to digital interventions, can facilitate progress.[98–100] Such evolving tools, which may include smartphone apps, virtual reality, social media, chatbots, and the use of big data and machine learning approaches to electronic health record processing and digital phenotyping, are certain to play an important role in individualizing psychiatric care. Digital tools offer the opportunity for improved prevention, screening, and monitoring of symptom severity and response to treatment,[101,102] smoking cessation,[103] promotion of desired behavioral changes such as increased exercise,[104] and augmentation of pharmacotherapy by improving adherence,[105,106] psychoeducation, and peer support, among others.[100] In addition, online-delivered approaches, including telepsychiatry, may have the potential to be more cost-effective and destigmatizing, making them particularly attractive in low-resource settings with limited access to mental health care.[107,108] For example, clustering of mobile sensor data can be used to detect routine and atypical behavioral trends associated with impending psychotic relapse in patients with schizophrenia.[109] While this is still an evolving area, and not entirely within the scope of this paper, it is not difficult to imagine that we will be able to progressively obtain better markers of complex human behaviors and related emotional and cognitive states that characterize mental health and illness states to support the individualization of mental health care. Importantly, these new developments will be integrated with shared decision making and other aspects of chronic disease management,[110] while respecting the patient's own cultural environment.[111] It is not far-fetched to imagine that in the future, mental health providers and care systems will routinely use big data and machine learning approaches, while integrating clinical assessments with electronic health records and sensor-guided phenotyping to individually characterize patients and guide and adapt treatment selection.

Several limitations need to be taken into account regarding this Delphi consensus project. First, the group of experts was limited. Second, the topics selected for consensus were selective and other topics may also be relevant. Third, recommendations are based on the current knowledge that is mostly based on self-reports, informant reports, interviews and behavioral observations without sufficient reliance on measurement-based care in routine psychiatric settings.[32,38] Fourth, as new data emerge, the current recommendations may need to be updated. Finally, these recommendations are not clinical guidelines and clinicians should refer to their national prescribing and practice guidelines to further inform their clinical decision-making process.

Conclusion

The approach of individualized psychiatry can already help mitigate the negative effects of current trial-and-error approaches in clinical practice, but more precise data generation, scalable tools, and implementation efforts are needed. Repeated unsuccessful pharmacologic and non-pharmacologic treatment trials lead to delays in achieving effective treatment, unnecessarily prolong personal, family, and societal suffering, potentially adversely affect disease course, and undermine patient engagement with the healthcare system, which is critical in schizophrenia. Individualized psychiatry offers a way to select and implement effective, more tailored treatments that take into account an individual's clinical characteristics, illness history and trajectory, family and social environment, and goals, desires, and preferences, including the avoidance or minimization of specific side effects, to maximize the overall chances of success.

Funding

This work was realized with an unrestricted educational grant from Angelini Pharma.

Disclosure

Dr Guinart has been a consultant and/or speaker for Otsuka, Janssen, Lundbeck and Teva. Prof Fagiolini has been a consultant and/or a speaker and/or has received research grants from Angelini, Apsen, Boheringer Ingelheim, Daiichi Sankyo, Doc Generici, Glaxo Smith Kline, Italfarmaco, Lundbeck, Janssen, Mylan, Neuraxpharm, Otsuka, Pfizer, Recordati, Rovi, Sanofi Aventis, Sunovion, and Vifor. Prof. Fusar-Poli has received grant fees from Lundbeck and honoraria from Lundbeck, Menarini and Angelini. Dr. Giordano has been a consultant for Angelini. Prof Leucht has received honoraria for service as a consultant or adviser and/or for lectures from Angelini, Böehringer Ingelheim, Geodon & Richter, Janssen, Johnson&Johnson, Lundbeck, LTS Lohmann, MSD, Otsuka, Recordati, SanofAventis, Sandoz, Sunovion, TEVA, ROVI and EISAI. Prof. Moreno has received honoraria as a consultant and/or advisor and/or for lectures from Angelini, British Association of Psychopharmacology (BAP), Compass, Esteve, Exeltis Janssen, Lundbeck, Neuraxpharm, Nuvelution, Otsuka, Pfizer, Servier and Sunovion outside the submitted work. Prof Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Tolmar, Vertex, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic. The authors report no other conflicts of interest in this work.

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