CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES
&
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QUARTERLY NEWSLETTER

Schizophrenia and Second Generation Antipsychotics—Applying Order to Chaos When Considering Receptor Specificity

Schizophrenia is a chronic mental health disorder characterized by psychotic episodes and cognitive symptoms which recur repeatedly over a patient's lifetime. The three major hallmark symptom categories of schizophrenia are positive symptoms, negative symptoms, and cognitive symptoms (Table 1).[1,2] Schizophrenia affects every aspect of a patient's life including family and social interaction, employment and education, mental and physical health, as well as social service, criminal and judicial involvement.

While the etiology of schizophrenia is not completely understood, there are several biological theories that attempt to explain it two of which are the dopamine theory and the glutamate theory, both concluding that excessive amounts of dopamine in the brain contribute to the symptoms of schizophrenia. The dopamine theory explains that excessive amounts of dopaminergic transmission occurs in the mesolimbic and striatal brain regions (accounting for positive symptoms) with lower dopamine amounts in the mesocortical brain region (accounting for negative symptoms). The glutamate theory centers around NMDA receptor hypofunctioning and prevention of glutamate from exerting its full effect which in turn prevents the release of gamma-aminobutyric acid (GABA) thus creating an excess of dopamine in the mesolimbic brain region and nucleus accumbens.[3] With the development of the second generation antipsychotics (SGAs), serotonin 5-HT_{2A} receptor blockade is also thought to have a downstream effect on decreasing dopamine levels in the brain.[4]

Biology alone does not cause schizophrenia but rather preexisting biology coupled with stress early on in a patient's life contribute to the development of this disorder.[1] Schizophrenia typically presents in late adolescence or the early twenties and the DSM-5 diagnostic criteria are described below. For a patient to be diagnosed with schizophrenia they must meet the following:[5]

A. **Two** or more of the characteristic symptoms below are present for a significant portion of time during a one-month period (or less if successfully treated):

- Delusions
- Hallucinations
- Disorganized speech (i.e., frequent derailment or incoherence)
- Grossly disorganized or catatonic behavior
- Negative symptoms (i.e., affective flattening, alogia, or avolition)

B. For a significant portion of time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to onset. When the onset is in childhood or adolescence: failure to achieve expected level of interpersonal, academic, or occupational achievement.

C. Continuous signs of the disturbance persist for at least six months. The six-month period must include at least one month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms, or two or more symptoms listed in Criterion A that present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either: (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse or medication) or a general medical condition.

F. If the patient has a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

The prevalence of schizophrenia in the United Stated is estimated to be 0.25% -

Table 1. Hallmark Symptoms of Schizophrenia

Positive Symptoms	Negative Symptoms	Cognitive Symptoms
♦ Psychosis ♦ Hallucinations ♦ Delusions	♦ Disrupted Emotion and behavior ♦ Anhedonia ♦ Lack of motivation (avolition) ♦ Flat affect	♦ Attention/memory deficits Verbal/visual learning deficits ♦ Memory deficits ♦ Impaired executive functioning ♦ Impaired problem solving and social cognition

0.64%.[6] During the previous one year of claims, 1.16% of the Connecticut Medical Assistance Program population received a diagnosis of schizophrenia. About half of all patients with schizophrenia have a comorbid mental health disorder such as anxiety or depression and up to 30% of patients may have a poor response or resistance to their medication treatment.[6,7] Patients with schizophrenia experience a shorter lifespan of about 28.5 years.[8] Contributing to this decline in years lived are metabolic issues, cardiovascular disease, comorbid disorders, and lifestyle choices.[8] Cardiovascular disease, including coronary artery and cerebrovascular disease, are the leading causes of death in patients with severe mental health disorders.[9] Patients with schizophrenia experience an increased risk of cardiovascular disease and metabolic disorder from two distinct sources; lifestyle factors and antipsychotic medication use. The nature of schizophrenia provides an opportunity for negative choices such as sedentary lifestyle, smoking, substance abuse, poor diet, lack of exercise, and high stress due to psychotic symptoms while SGAs contribute to cardiovascular disease and metabolic syndrome on their own.[10]

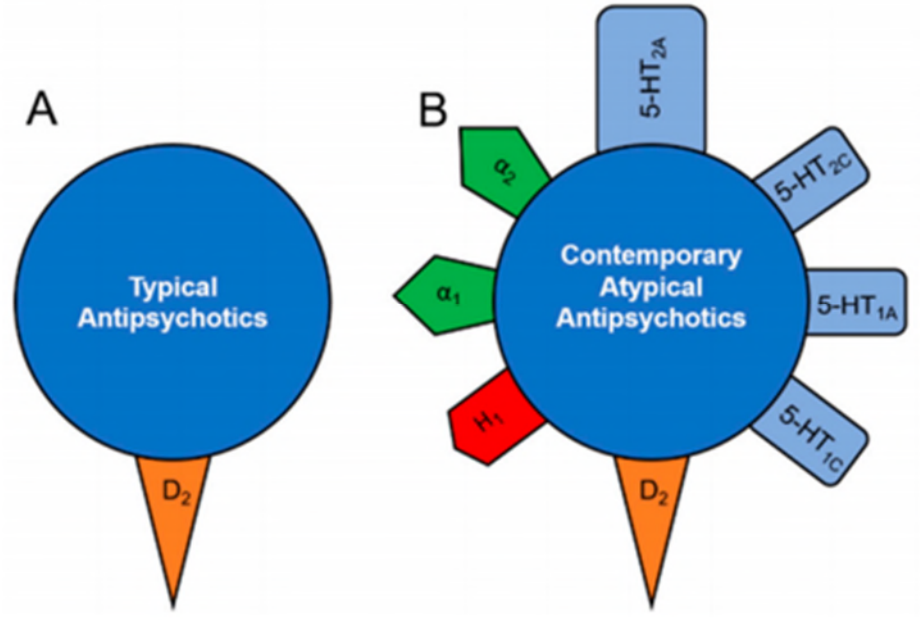
Antipsychotic medications are the gold standard for the treatment of schizophrenia. There are two general classes of antipsychotics typical, or first generation antipsychotics (FGAs) and atypical, or SGAs.

Chlorpromazine was the first antipsychotic to be developed in 1950 and was followed by many other FGAs which are effective at treating positive symptoms of schizophrenia.[11] All FGAs are potent dopamine D_2 antagonists which make them very effective at treatment but simultaneously cause adverse effects associated with D_2 antagonism such as cognitive and neuromuscular side effects, and hyperprolactinemia. Due to the sedation, extrapyramidal side effects (EPS), and tardive dyskinesia (TD) caused by the FGAs, the scientific community saw a need to develop alternative therapies with less severe side effects.[11]

Clozapine, a tricyclic dibenzodiazepine and first SGA, was synthesized in 1959 out of research intended to create additional treatment options for depression. Clozapine was not a strong or effective antidepressant but was found to possess antipsychotic activity.[12] In 1975, a study showed that clozapine had a detrimental effect on neutrophils, causing fatal agranulocytosis in 8 patients.[13] This study shelved the use of clozapine until 1988 when the Clozapine Collaborative Group Study highlighted the overwhelming effectiveness of clozapine for treatment resistant schizophrenia (30% responded to treatment), while having beneficial effects on both positive and negative symptoms, with little to no EPS/TD development. The caveat with clozapine treatment was the need for appropriate hematological monitoring for agranulocytosis, an adverse event unique to this medication.[14,15] Clozapine was considered a novelty compared to the FGAs proving that antipsychotics didn't need to possess potent D_2 blocking abilities to be effective treatment options for schizophrenia. However, while it is the most effective SGA to date in patients not responsive to other antipsychotics, due to its side effect profile, specifically sedation, weight gain, and agranulocytosis, only a small percentage of patients eligible to receive clozapine treatment go on to do so. Clozapine remains the most effective treatment for schizophrenia on the market and is the gold standard for treatment resistant schizophrenia.

Between 1993 and 2006, many more SGAs were developed.[16] While initially indicated for schizophrenia, the SGAs today treat a wide range of psychiatric disorders including other psychotic disorders, bipolar disorder, adjunctive treatment for treatment resistant depression, anxiety, insomnia, agitation, and aggression.[17,18] Currently, there are 13 SGAs on the market (Table 2) and while their mechanisms of action share similarities, receptor and synaptic targets differ for each agent providing unique profiles of distinct adverse reactions and side effects. SGAs have less dopamine blocking at the D_2 receptors than most FGAs and therefore have fewer side effects associated with D_2 antagonism.[4] SGAs have binding affinity to $5HT_{2A}$ receptors often equivalent to or more so than their D_2 affinity. SGAs are also known to target other dopamine receptors (D_1 and D_3), other serotonin receptors ($5HT_{1A}$, $5HT_{1c}$, $5HT_{1D}$, $5HT_{2C}$, $5HT_6$, $5HT_7$), muscarinic receptors (M_1, M_3), histamine receptors (H_1), and adrenergic receptors (α_1 and α_2).[11,19,20] The unique combination of receptor binding and affinity dictates the side effect profile seen with each product. Binding affinity can be viewed as a spectrum, some SGAs bind more tightly to a receptor than others, causing greater effect but also more severe side effects when affinity is higher.

When considering treatment with SGAs, initial response is typically seen within the first 2 weeks but can take up to 4-6 weeks to reach full efficacy. Patients experiencing their first schizophrenic episode often require lower doses of antipsychotics, are



responsive to treatment, but may be more susceptible to adverse effects.[21] If response is not clinically evident after an appropriate trial period, it is recommended to increase the dose or change to a different medication.[21] If a patient responds to treatment but adverse events emerge, decreasing the dose or changing agents if the adverse event is unmanageable is appropriate.[21] When selecting an agent for use consideration of unique side effect profiles should be weighed. With the exception of clozapine, the other SGAs have comparable efficacy, all of which have been found to be better than placebo.[21] Often times when selecting treatment options, weighing the side effect profile of each agent and considering patient preference is important. Below are some common side effects seen with SGAs.

Metabolic syndrome

Metabolic syndrome is associated with an increase in waist circumference, weight gain, elevated cholesterol levels (including triglycerides), a decrease in high-density lipoproteins (HDL), hypertension, and increased fasting glucose levels.[22] Both low potency FGAs such as chlorpromazine as well as all SGAs can cause metabolic syndrome. It is not completely understood why these agents cause metabolic syndrome and weight gain but theories include the involvement of multiple receptors increasing appetite via hypothalamic homeostasis (histamine, serotonin, dopamine, and muscarinic), induction of insulin sensitivity, decrease in metabolism, and somnolence from medication therapy causing sedentary behavior.[11,23] Weight gain and effect on insulin and glucose is typically seen in the first few weeks of treatment or early in the course of therapy, especially in younger patients who are treatment naïve or in older patients.[10,24-26] Approximately 50% of patients who receive treatment with SGAs will go on to develop metabolic side effects.[27,28] Interestingly, SGAs can have a direct effect on insulin resistance and glucose regulation independent of weight gain. In 2003, the FDA required drug makers to include a warning in their package inserts regarding the risk of hyperglycemia and diabetes. Clozapine and olanzapine are associated with the greatest risk of weight gain and metabolic syndrome but are also the most effective treatment options for schizophrenia.[11,29] SGAs with the lowest risk of metabolic issues include lurasidone, ziprasidone, and aripiprazole.[11,29] Recommended monitoring for all SGAs include baseline and subsequent BMI (Body Mass Index) during each visit or at least every 6 months, random glucose monitoring, baseline lipid panel, and ECG (Electrocardiogram).

Cardiac side effects

Orthostatic hypotension is a risk associated with SGAs, particularly with those that have a high affinity for α-1 receptor blockade such as clozapine, quetiapine, and iloperidone. Patients who are at greatest risk of developing orthostatic hypotension are the elderly, diabetic patients, and patients who are volume depleted. Orthostatic hypotension causes syncope and falls which can be especially detrimental in the elderly population. SGA choice, low dose selection, and slow dose titration can help prevent this side effect from occurring.[30]

QTc prolongation and sudden cardiac arrest are adverse events associated with antipsychotic use. Antipsychotics have a 2-4 times greater risk of causing sudden cardiac death compared to the general population and is thought to occur via QT prolongation leading to fatal ventricular tachycardia, known as torsades de pointes.[30,31] Risk factors for developing QTc prolongation with SGA use include dose antipsychotic medication, concurrent medications that cause QTc prolongation, electrolyte imbalance, preexisting hypertension, ischemic heart disease, hepatic or renal impairment, advanced age, and female gender. It is recommended to obtain a baseline ECG prior to initiating treatment with SGAs and to repeat periodically. Ziprasidone and risperidone show the greatest risk of QTc prolongation and sudden death, respectively.[30,31]

Clozapine induced myocarditis can lead to cardiomyopathy and congestive heart failure. Cardiomyopathy is a rare side effect only occurring in 0.02-0.1% of patients treated with clozapine with a mortality rate of up to 18%. If myocarditis occurs, it generally happens during the first two months of therapy. It is recommended to start at the lowest effective dose and titrate slowly while monitoring for symptoms such as chest pain, palpitations, dyspnea, and edema. If clozapine induced myocarditis/myopathy is suspected, it is recommended to perform an ECG and

Table 2 SGA Receptor Binding Affinities

Antipsychotic	Dopamine (D2) blockade	Histamine (H1) blockade	Alpha-1 blockade	Muscarinic (M1) blockade
Clinical effects	EPS, akathisia	Sedation, weight gain	Orthostatic hypotension	Dry mouth, blurred vision, urinary retention constipation
Aripiprazole (Abilify)[1]	++++	++	++	-
Asenapine (Saphris)	+++	+++	+++	+
Brexpiprazole (Rexulti)[1]	+++	++	+++	-
Cariprazine (Vraylar)[1]	++++	++	++	-
Clozapine (Clozaril)	+	++++	++++	++++
Iloperidone (Fanapt)	+++	++	+++	-
Lumateperone (Caplyta)	+++	+	+++	+
Lurasidone (Latuda)	+++	-	++	-
Olanzapine (Zyprexa)	++	+++	+	+++
Paliperidone (Invega)	+++	+	+++	-
Quetiapine (Seroquel)	+	+++	+++	+
Risperidone (Risperdal)	+++	+	+++	-
Ziprasidone (Geodon)	+++	+	+	-

+weak binding affinity; ++++ strong binding affinity; [1]partial D2 agonist activity

Gable KN. Antipsychotic polypharmacy: helpful or harmful. *The Carlat Psychiatry Report. 2015;4(1).*

discontinue therapy. Termination of therapy causes a return to normal cardiac functioning for most patients. Re-initiation of clozapine has a high rate of myocarditis/myopathy recurrence, therefore, if clozapine therapy benefits outweigh the risk of myopathy, re-initiation should occur under close medical supervision.[30-32]

Secondary elevated prolactin levels due to D_2 antagonism

Sexual side effects associated with antipsychotic treatment include decreased libido, erectile and ejaculatory dysfunction, gynecomastia in men, vaginal dryness and amenorrhea in women, and inability to orgasm.[33] SGAs cause these effects through D_2 antagonism and secondary hyperprolactinemia. SGAs with high affinity for D_2 receptors (risperidone and paliperidone) cause higher rates of sexual side effects compared to SGAs with lower D_2 affinity (aripiprazole, clozapine, olanzapine, quetiapine).[33] Sexual side effects can have a negative impact on quality of life and can increase nonadherence.

Using a questionnaire to assess adverse events assists in evaluating troublesome side effects patients may not realize are connected to SGA treatment or otherwise feel uncomfortable discussing. Using a side effect questionnaire such as the Glasgow Antipsychotic Side Effect Scale (GASS) and the GASS for Clozapine (GASS-C) are good options for self-screening. They are short, straightforward surveys that encompass all types of adverse events associated with SGAs as well as frequency and level of distress associated with each side effect.[34,35] If a patient perceives a side effect as distressing, it should be addressed as adherence to medications and overall treatment experience will be affected.[36]

A decrease in bone mineral density (BMD) and increased risk of fracture is associated with antipsychotic medications with high affinity for the D_2 receptor. Dopamine, under normal circumstances, works to suppress prolactin secretion by the pituitary gland. SGAs, especially agents with high affinity for the D_2 receptor (risperidone and paliperidone) block dopamine and decrease levels in the brain causing the pituitary to secrete prolactin unchecked. This causes a downstream effect, lowering calcium absorption and increasing bone resorption.[37] It is recommended to monitor patient prolactin levels, provide vitamin D supplements, and use the lowest effect dose of antipsychotic to circumvent a decline in BMD.

Movement disorders such as akathisia, dystonic reactions, EPS, and TD are associated with antipsychotic use and D_2 antagonism. The greater the D_2 blockade and length of treatment, the greater the risk of developing a movement disorder. It has been estimated that 32% of patients receiving FGAs will develop TD, whereas 13% of patients receiving SGAs will develop TD. Patients who receive chronic therapy at high doses are at the greatest risk and even if the offending agent is stopped, TD can persist.[38,39] While SGAs in general have a lower risk of causing movement disorders compared to FGAs, clozapine and quetiapine have the lowest risk as they dissociate quickly from D_2 receptors.[4] Recently, the FDA has approved two vesicular monoamine transporter 2 (VMAT2) inhibitors to treat TD, Deutetrabenazine (DBZ) and Valbenazine (VBZ). Prior to their approval, treatment of TD was limited to the off-labeled use of clonazepam, dopamine agonists or ginkgo biloba.[30]

Sedation/somnolence

Sedation and somnolence associated with SGAs originates from the use of high doses as well as the individual drug affinity for histamine H_1 receptors. Clozapine is classified as causing high somnolence whereas olanzapine, quetiapine, risperidone, and ziprasidone are classified as causing moderate somnolence. Asenapine, aripiprazole, cariprazine, lurasidone, and paliperidone are considered to have a low risk of somnolence.[40] It is widely known that patients suffering from schizophrenia experience a spectrum of sleep disturbances ranging from excessive sleepiness to insomnia. Sedation and somnolence caused by SGAs can be used to benefit patients in certain circumstances. The use of high or moderate somnolence SGAs can be trialed in schizophrenic patients who suffer from insomnia, dosing these medications at night. Inversely, patients who are combatting excessive sleepiness may benefit from SGAs with lower H_1 affinity, promoting more wakefulness.

Anticholinergic side effects

Anticholinergic side effects are thought to be associated with SGAs affinity for muscarinic M_1 receptors. Anticholinergic side effects present as dry mouth, blurred vision, retention of urine, constipation, and in more severe cases confusion. Clozapine, quetiapine, and olanzapine have been associated with higher rates of anticholinergic side effects. It is recommended that if patients develop these side effects, to lower the dose of the SGA or switch to an agent that is not associated with muscarinic blockade.

SGAs in the elderly

Widespread use of SGAs in older adults is a concern due to the increased risk of adverse events and death. In previous years, SGAs were commonly used off label to treat dementia related psychiatric symptoms, however, in 2005, the FDA required all SGAs to carry a black box warning against the use of these agents in elderly patients with dementia as they showed an increased risk of stroke and death. In 2008, the FDA extended this warning to encompass all antipsychotics. The American Geriatric Society Beers criteria recommends avoiding the use of antipsychotics for the treatment of dementia related neuropsychiatric symptoms and the American Psychiatric Association published recommendations to prescribe antipsychotic medications to patients with dementia only if behavioral issues are severe enough to cause harm to the patient or others.[41,42] Since these warnings were published, the use of SGAs in the elderly has declined significantly. In addition to the increased risk of stroke and death, elderly patients are also more susceptible to other SGA adverse events such as α mediated orthostatic hypotension and anticholinergic effects.

SGAs in the pediatric population

Similar to the elderly population, children have a higher risk of SGA mediated adverse events including the increased risk of lifetime diabetes, metabolic syndrome, and cardiovascular disease.[17] A 2019 article published in the Journal of Pediatrics found that 5 adverse drug reactions associated with SGAs had a higher incidence of occurring in the pediatric population versus adults.[43] The largest 5 risk difference adverse drug reactions were sedation with risperidone, weight increase with olanzapine, sedation with queti-

apine, sedation with asenapine, and fatigue with risperidone. This information illustrates that while safety studies in adults can be extrapolated to pediatrics, certain adverse drug events may occur differently and at higher rates in the pediatric population when compared to adults. Sedation, weight gain, and fatigue can have negative effects in children presenting as learning disabilities and decreased motivation to learn in school. This may have a negative effect on tolerance and adherence which pediatricians should be aware of when prescribing these medications.[43] Monitoring of BMI, glucose, and lipids in children should be performed regularly.

SGAs in pregnancy

There has been an increase in the use of antipsychotics in pregnant women. Park et al reported that in 2001, 0.4% of Medicaid insured women received SGAs during pregnancy whereas 1.3% of pregnant women enrolled in Medicaid received SGAs during 2010.[44] Pregnant women who received treatment were found to have a higher incidence of obesity, illicit drug use, alcohol use, smoking, and use of other medications to treat psychiatric disorders both prior to and during pregnancy.[44] Due to these compounding variables there may be an increased risk of adverse fetal effects independent of SGA use, however, pregnant women who stop antipsychotic treatment are at an increased risk of psychiatric relapse. It has been reported that schizophrenic patients who stop treatment are 53% more likely to experience disease symptom worsening within a 10 month timeframe.[45] Pregnant women who stop antipsychotic treatment are also risking harm to the fetus such as low birth weight, fetal distress, small gestational age, disorder attachment, and delayed development.[45] Untreated mental disorders in pregnant women can also lead to risky behavior during pregnancy such as drug and alcohol use, sexual promiscuity, and unmet prenatal care. The decision to treat pregnant women with SGAs is a risk versus benefit decision that should be weighed carefully.

Typical antipsychotics (haloperidol and perphenazine) have been used safely in pregnancy to treat mental health disorders. Perphenazine can also be used as an antiemetic. Quetiapine is the most prescribed SGA in pregnancy with aripiprazole being the second most prescribed. Quetiapine does not show an increase in birth defects or malformations whereas aripiprazole may increase the risk of gastrointestinal deformities such as palate or esoghageal malformations.[45] Information available on olanzapine and ziprasidone show they are not associated with congenital malformations. Clozapine, asenapine, brexpiprazole, cariprazine, and iloperidone do not have enough data regarding the risk of use in pregnancy and lactation. While lurasidone is rated pregnancy category B due to favorable animal studies, there is not enough information regarding its use in humans during pregnancy.[45] Risperidone and paliperidone have mixed data on the risk of congenital defects and are not recommended as first line agents in pregnancy.

In summary, common side effects associated with SGAs include metabolic syndrome, cardiovascular effects, sexual side effects, sedation, and anticholinergic effects. Additionally, it should be noted that antipsychotics are associated with an increased risk of falls, pneumonia, agranulocytosis (clozapine), QT prolongation, ventricular tachycardia, and sudden death.[46-51] Adverse events can increase morbidity and mortality, while decreasing quality of life, tolerance, and adherence. Apart from clozapine, there is little evidence showing one SGA is more efficacious than another. Clinical judgement, patient specific factors (prior therapies, tolerability, preference, cost), adverse effects, drug interactions, symptom control, and comorbid conditions should be considered when selecting therapy. Providing information to patients on both the frequency of side effects as well as the most distressing side effects of each medication can assist with selection. Once treatment is started, setting expectations, regular check ins, and monitoring side effects with appropriate screening tools can boost medication adherence. Coordination of care with other health care providers, addressing lifestyle modifications, and assessing patient social support networks can also lead to better adherence and patient outcomes. Mental health disorders that require SGA treatment are typically lifelong illnesses. If a negative outlook on medication treatment or disease state exists, it can last a lifetime. As clinicians become more aware of the adverse effects SGAs can pose on physical health, this should guide clinical judgement and decision making processes for medication selection for the individual. Medications should treat the whole patient, not just the disease. Consideration of both the mental and physical health of the individual patient is paramount.

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