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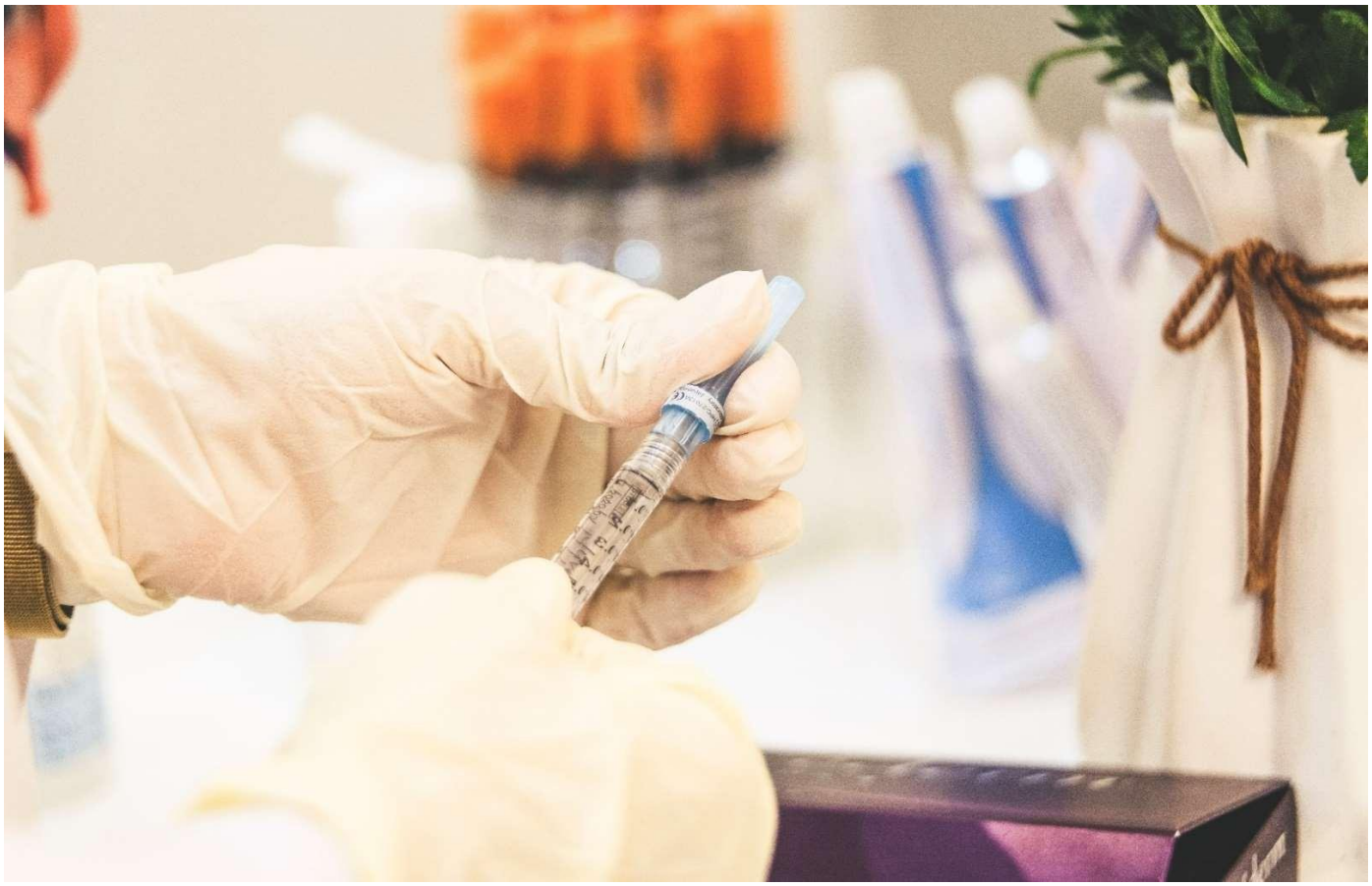
Second-generation antipsychotics and extrapyramidal adverse events



Introduction

Second-generation antipsychotics were initially believed to have a lower propensity to cause EPS due to their atypical mechanisms of action and reduced affinity for dopamine receptors. However, various studies have shown that EPS can still occur with second-generation agents, albeit at lower rates compared to first-generation drugs. Risk factors for EPS with second-generation antipsychotics include the specific drug chosen (with clozapine having the lowest risk and risperidone the highest), high dosages, a history of previous EPS symptoms, and comorbidities. Additionally, the selection of the first-generation comparator in comparative studies significantly influences the findings. Despite the introduction of second-generation antipsychotics, EPS remains clinically relevant, and these drugs have not entirely fulfilled expectations regarding their tolerability in this regard. Clinicians should be vigilant in monitoring for EPS symptoms and consider individual factors when choosing antipsychotic medications to minimize the risk of EPS.

Background

Indeed, the development of second-generation antipsychotics (SGAs) represented a significant advancement in the treatment of schizophrenia and challenged the traditional understanding of antipsychotic pharmacology. The introduction of chlorpromazine in 1952 marked the beginning of antipsychotic drug therapy, and while effective in treating positive symptoms of schizophrenia, first-generation antipsychotics (FGAs) like chlorpromazine, haloperidol, and fluphenazine had limitations. They were not very effective against negative symptoms of the disease and were associated with serious adverse effects, particularly extrapyramidal symptoms (EPS), which were linked to their dopamine D2 receptor blockade.

However, the discovery and clinical success of clozapine as the first second-generation antipsychotic (SGA) demonstrated that it was possible to achieve antipsychotic efficacy without causing EPS. Clozapine was highly effective, even in treatment-resistant schizophrenia, but it was notably associated with the risk of agranulocytosis, a potentially life-threatening decrease in white blood cells. Despite this drawback, clozapine's success provided a model for the development of other SGAs with a more favorable side effect profile.

One of the key differences between FGAs and SGAs lies in their receptor profiles. While all antipsychotics have some level of antagonistic affinity for dopaminergic D2 receptors, SGAs were found to have a higher affinity for certain serotonin receptors (mostly 5HT2A receptors) compared to D2 receptors. This serotonin-dopamine receptor balance is thought to be crucial in the reduced propensity of SGAs to cause EPS.

The traditional dopamine hypothesis of schizophrenia, which posited that dopamine D2 receptor blockade was essential for the antipsychotic effect but also responsible for EPS, was challenged by the clinical success of SGAs. Clozapine, as the prototype SGA, demonstrated that strong D2 receptor blockade was not necessary for antipsychotic efficacy. Instead, SGAs appeared to have a unique binding profile to D2 receptors, characterized by loose binding and fast dissociation, which may contribute to their lower EPS risk.

It's important to note that while SGAs have shown clear benefits in reducing EPS, they are not completely devoid of side effects. Each SGA has its own unique receptor-binding profile and side effect profile, which means that individual responses to different SGAs may vary.

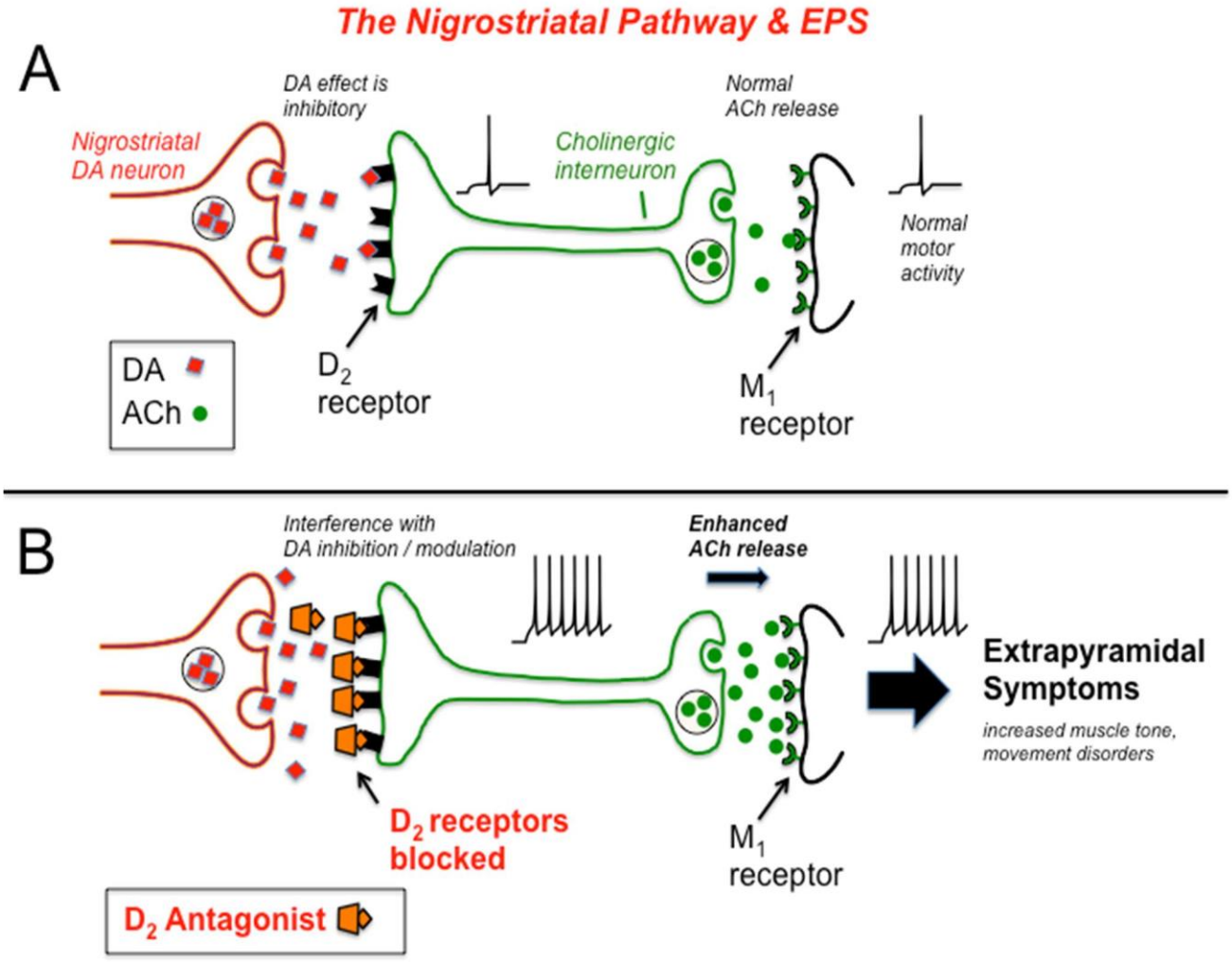
Overall, the development of SGAs represented a significant advancement in the treatment of schizophrenia, offering improved efficacy and a more favorable side effect profile compared to FGAs. However, it's essential for healthcare professionals to carefully consider the individual patient's needs and characteristics when selecting the most appropriate antipsychotic medication.

The effectiveness of pharmacological treatments for schizophrenia cannot be properly assessed without considering their potential adverse effects. Second-generation antipsychotics (SGAs) were initially hailed for their improved tolerability compared to first-generation antipsychotics (FGAs), especially in terms of reducing extrapyramidal side effects (EPS). The idea of treating schizophrenia without causing EPS was highly desirable for both mental health professionals and patients. However, post-clozapine SGAs have not completely met these expectations, as EPS still pose a significant problem in schizophrenia treatment. Recent clinical trials and meta-analyses have demonstrated that, with the exception of clozapine, all SGAs have a tendency to induce certain levels of EPS. Furthermore, postmarketing surveillance has brought to light additional adverse effects associated with SGAs, such as weight gain and metabolic side effects. However, it is important to note that FGAs also contribute to notable metabolic side effects, and the prevailing belief that SGAs solely cause metabolic side effects while FGAs lead to EPS is not supported by recent findings. This review aims to summarize the most recent reported results regarding the risk of EPS development in patients treated with different classes of antipsychotic drugs, challenging the oversimplified classification of antipsychotic drug classes and emphasizing the need for a more nuanced understanding of their respective adverse effects profiles.

Table 1
First- and second-generation antipsychotics and D2 antagonism.

Antagonistic D2 effect	First-generation antipsychotics		Second-generation antipsychotics
Low	Chlorpromazine Thioridazine	Levomepromazine	Clozapine Quetiapine

Intermediate	Trifluoperazine Perphenazine	Olanzapine
High	Haloperidol Fluphenazine Flupentixol	Risperidone Ziprasidone Aripiprazole (possible D2 agonism)



Extrapyramidal symptoms

EPS encompass a range of serious and sometimes debilitating adverse effects associated with antipsychotic medications, including acute dystonias, akathisia, Parkinsonism, and tardive dyskinesia (TD). These effects can be stigmatizing and may require additional pharmacotherapy to manage. EPS can be categorized into two phases: early, acute EPS, which often occurs when initiating or increasing antipsychotic treatment, and later-onset EPS, commonly presenting as TD, which may appear after prolonged treatment.

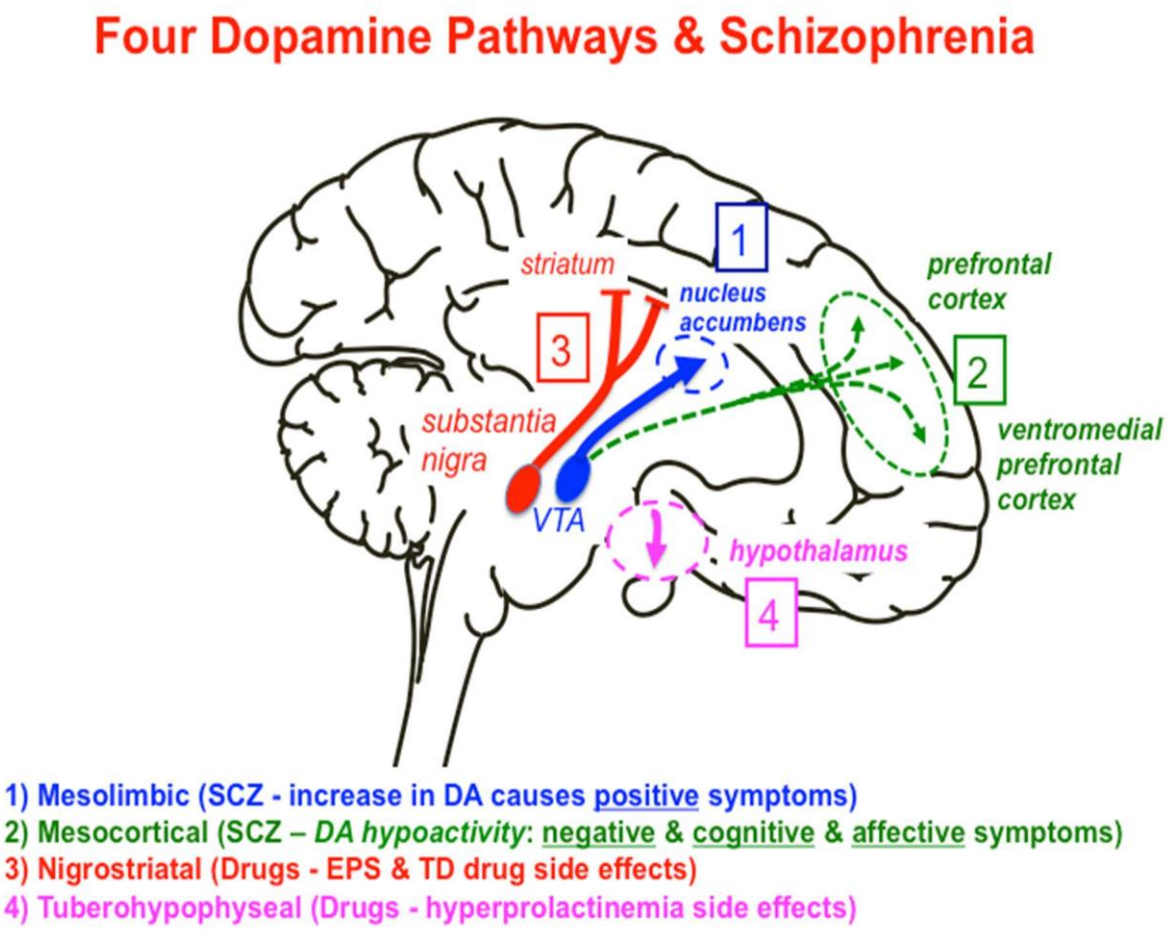
Acute EPS typically manifest as akathisia, acute dystonia, and Parkinsonism. Akathisia involves restlessness and pacing, acute dystonia is characterized by abnormal sustained postures and muscle spasms, often affecting the head or neck, while Parkinsonism presents as tremors, skeletal muscle rigidity, and/or bradykinesia. TD, on the other hand, involves involuntary and repetitive facial movements like grimacing, tongue protrusion, oculogyric crises, and puckering of the lips, as well as movements of the torso and limbs. The reversibility of acute EPS symptoms is one of the main factors contributing to poor adherence to antipsychotic treatment, while TD, especially when late-onset, significantly impacts the quality of life of patients and their caregivers. TD may persist even after discontinuing the medication and, in some cases, become irreversible.

The prevalence of acute EPS varies among different studies and antipsychotic medications. For instance, approximately 50% of patients treated with high-potency first-generation antipsychotics (FGAs) like haloperidol may develop acute EPS within the first few days of treatment. However, the prevalence of TD is more difficult to ascertain due to methodological differences among studies, with reported rates ranging from 0.5% to 70% of patients receiving FGAs, and an average rate of 24% to 30%.

Management of acute EPS often involves reducing the dosage of the antipsychotic or administering additional pharmacological treatment. Acute dystonia, for instance, can be effectively prevented or reversed using anticholinergic drugs like biperiden. Risk factors for acute dystonia include young age, male gender, history of substance abuse, and a family history of dystonia. It is more common with FGAs like haloperidol and less so with second-generation antipsychotics (SGAs). However, some case reports have described acute dystonia after initiation of antipsychotic treatment with aripiprazole and ziprasidone.

Akathisia is a common and challenging EPS to manage, occurring in approximately half of all cases. It is more prevalent within the first three months of treatment and does not typically respond to anticholinergic medication. Instead, antipsychotic dose reduction, liposoluble beta-adrenergic blockers, and benzodiazepines have shown effectiveness in treating akathisia. Rough estimates suggest that around 25% of patients treated with FGAs experience akathisia, but it is also common with SGAs. Some research indicates that akathisia rates do not significantly differ between FGAs and SGAs. Studies have previously suggested that certain SGAs, such as clozapine and quetiapine, carry the lowest risk for akathisia, but this finding has not been consistently confirmed in all reviews.

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared multiple SGAs with the FGA perphenazine, it was shown that akathisia remains an issue with SGAs, albeit at lower rates compared to FGAs. The study revealed no significant difference in the incidence of akathisia and other EPS among the antipsychotics tested during long-term treatment for up to 18 months in patients with chronic schizophrenia. However, it's essential to consider the limitations of the CATIE study, such as the use of an intermediate-potency FGA (perphenazine) and non-randomized allocation of patients with TD to SGA treatment, when interpreting these findings.



Conclusion

Second-generation antipsychotics (SGAs) were initially expected to be free from extrapyramidal syndrome (EPS) side effects and were recommended as first-line therapy for schizophrenia. However, recent studies have shown that SGAs have not fully lived up to this expectation. While they generally have a lower propensity to cause EPS compared to first-generation antipsychotics (FGAs), the superiority of SGAs in terms of efficacy and tolerability is not entirely clear.

Current guidelines recommend SGAs as the preferred choice for treating schizophrenia, except for clozapine, which is reserved for treatment-resistant cases. However, recent research indicates that SGAs do not significantly differ from FGAs in terms of overall efficacy, except for clozapine's exceptional efficacy in treatment-resistant cases. Moreover, there is considerable variability within the SGA class regarding their propensity to cause EPS.

Several factors influence the likelihood of EPS occurring with an SGA. Patient-specific characteristics, such as age, gender, and concurrent medical conditions, as well as the patient's history of the disease and previous treatments, play a role. Additionally, the choice of a specific SGA, its dosage, the duration of treatment, and any adjuvant therapies should be carefully considered to minimize the risk of EPS and provide optimal care.

At present, a trial-and-error approach is often recommended due to the unpredictability of therapeutic outcomes and adverse effects with antipsychotic medications. However, promising advances in pharmacogenomics (the study of how genetic variations influence drug responses) and neurobiology may offer predictive markers for antipsychotic response and adverse effects. Moving towards personalized therapy based on individual patient factors and genetic information could lead to more effective and safer treatment options.

In conclusion, while SGAs generally have a lower propensity to cause EPS compared to FGAs, they have not entirely eliminated the risk. The choice of the most appropriate antipsychotic should be individualized, considering various factors to achieve the best therapeutic outcomes while minimizing the occurrence of EPS and other adverse effects. Future research in pharmacogenomics and neurobiology may help tailor antipsychotic treatment for individual patients to improve overall care in schizophrenia management.

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Contact Us

INDIA: E13/9 First floor, Vasant Vihar, New Delhi 110057

NORTH AMERICA: 59 E, Shrewsbury Place Princeton, NJ 08540 United States

EU: Wilhelmina Druckerlaan 10, 6532 SR, Nijmegen, The Netherlands

LATIN AMERICA: Cerrada Ahuizotla 53, Col. Santiago Ahuizotla, Del. Azcapotzalco CP.02750 Ciudad de México, México

Business Enquiries: info@awinsals.com|www.awinsals.com

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