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Expanding Treatment Approaches for Schizophrenia: Beyond Antipsychotic Selection

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ABSTRACT

Over the past five decades, the treatment landscape for schizophrenia has predominantly revolved around the development of antipsychotic drugs. Despite notable advancements leading to the availability and utilization of numerous medications, they generally fall into three primary classes: conventional (typical), atypical, and dopamine partial agonist antipsychotics. While these drugs operate through diverse mechanisms of action, they predominantly target dopamine systems. Although second-generation (atypical and dopamine partial agonist) antipsychotics are perceived to offer advantages over first-generation agents, the distinctive pharmacological properties underlying the therapeutic effects of these newer drugs remain unclear. Furthermore, certain side effects persist, potentially impacting patient well-being and quality of life. Additionally, the efficacy of antipsychotic drugs is constrained, necessitating the adjunctive use of pharmacotherapy to enhance treatment outcomes. Despite ongoing efforts, the quest for novel non-dopaminergic antipsychotic drugs has yet to yield breakthroughs, although various development strategies persist, informed by diverse pathophysiologic hypotheses. This article offers a concise overview and critique of the current therapeutic arsenal for schizophrenia treatment, alongside drug development strategies and theories regarding the mechanisms of action of antipsychotics. Moreover, it directs attention toward novel targets for therapeutic agents in future drug development endeavors.

Keywords: Schizophrenia; Antipsychotic drugs; Psychosis; Hyperprolactinemia.

INTRODUCTION

English and Castle propose an updated set of Clinical Practice Guidelines (CPG) for schizophrenia and related disorders, endorsed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP). They suggest that these guidelines should be primarily shaped by the side-effect profiles and the potential for risk reduction offered by available antipsychotics. Given the comparable efficacy of most antipsychotics, this approach aligns with several contemporary international guidelines. Moreover, integrating the informed perspectives and preferences of patients in a shared decision-making process would be prudent [1].

The authors emphasize three key side effects of antipsychotics that are deemed physiologically significant:

- Tardive dyskinesia (TD).
- Metabolic syndrome (MetS).
- Hyperprolactinemia.

In the realm of psychotropics, there is arguably no clear distinction between "side" effects and effects; they are simply effects that can be interpreted as beneficial or adverse depending on the individual, timing, and circumstances. For instance, sedation induced by olanzapine might be deemed beneficial for someone struggling with psychosis or insomnia but adverse for someone preparing for a 9 am job interview. The term "side" implies the existence of a "central" effect, yet psychotropic drugs exert wide-ranging effects on various receptors across multiple brain regions, where beneficial effects are often intertwined with more global effects.

A prime example is the broad blockade of D2 receptors across multiple brain pathways by antipsychotics. While acutely targeting the mesolimbic pathway may alleviate positive psychotic symptoms, chronic blockade in the nigrostriatal pathway may contribute to the development of TD [2].

The treatment landscape for schizophrenia has traditionally revolved around antipsychotic medications, with a focus on managing side effects such as tardive dyskinesia (TD), metabolic syndrome (MetS), and hyperprolactinemia. English and Castle underscore the significance of these side effects, particularly TD, which is characterized by chronic, involuntary movements believed to stem from upregulation of D2 receptors in response to D2 blockade—a process termed "dopamine supersensitization." They suggest that partial D2 agonists like aripiprazole may carry a lower risk of TD, hinting at the potential of newer agents like brexpiprazole and cetirizine.

However, beyond TD lies the concept of Supersensitivity Psychosis (SP), a hypothetical phenomenon where a "supersensitized" mesolimbic pathway predisposes individuals to psychotic relapse [2-4]. Analogous to TD but affecting a different brain pathway, SP underscores the need to reconsider factors influencing the risk of both conditions. While antipsychotic choice is crucial, variables like dose, frequency, and duration of exposure are equally important yet often overlooked. Chouinard's proposed guidelines advocate prevention strategies such as monitoring with validated scales and using lower-risk

agents at lower doses. Additionally, emerging evidence supporting "minimal medication" approaches challenges conventional practices. Studies in Australia and the UK have shown comparable outcomes between minimal-medication approaches and antipsychotic treatment-as-usual, prompting the exploration of drug-free treatment programs in countries like Norway and the USA.

Renowned researcher Robin Murray suggests that a significant portion of individuals with first-episode psychosis (FEP) may achieve favorable long-term outcomes with minimal or no antipsychotic medication. While there are no perfect solutions, efforts to minimize neurochemical disturbances should remain a priority in schizophrenia treatment. As we navigate treatment paradigms, striving for better outcomes while mitigating risks remains paramount.

DISCUSSION

The discussion underscores the critical importance of the antipsychotic choice in treating psychosis, aligning with English and Castle's emphasis on minimizing the risks of adverse effects like TD, MetS, and hyperprolactinemia. However, the scope extends beyond the drug selection to encompass factors such as dosage, frequency, and treatment duration, especially considering the putative pathophysiology of both TD and SP [5,6].

The growing body of evidence supporting "minimal-medication" approaches for first-episode psychosis challenges existing guidelines advocating continuous antipsychotic treatment for 2-5 years. The call for individualized treatment plans reflects a paradigm shift, acknowledging that a psychopharmacological one-size-fits-all approach may not be universally applicable. Future clinical practice guidelines (CPGs) from organizations like RANZCP could consider incorporating this paradigm shift, allowing for tailored treatment strategies that prioritize patient well-being.

CONCLUSION

This discussion urges a reevaluation of the current therapeutic approaches, emphasizing the need for personalized treatment plans that consider both the risks and benefits of antipsychotic medications. The evolving landscape of schizophrenia treatment warrants ongoing exploration of novel targets and therapeutic agents to enhance future drug development.

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