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TREATMENTS OF SCHIZOPHRENICS IN ACUTE PSYCHIATRIC DISORDERS WITH ATYPICAL ANTIPSYCHOTIC MEDICATIONS (AAP)

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ABSTRACT

There are two types of atypical antipsychotic medications: AAP (atypical antipsychotics), and second-generation antipsychotics (second-generation antipsychotics). AAP are used to treat schizophrenia during acute psychoses, but they are also suggested for long-term maintenance. These medications differ from standard antipsychotics in that they have a distinct clinical profile and are less likely to produce extrapyramidal symptoms (EPS). This drug induces peripheral effects which lead to phenotypic, functional, and systemic alterations outside of the CNS despite its obvious therapeutic advantages (CNS). AAP is usually accompanied with metabolic illness, which has a major negative influence on the health and well-being of the patient. In addition to the immunological and endocrine systems, AAP therapy alters the gut micro biota, which can have clinical implications. These less well-researched changes also have a big influence on the health of the patient. Researchers hope to learn more about the effects of AAP intake on peripheral immune, endocrine, and intestinal micro biome alterations in patients with schizophrenia and other mental health conditions by revising current therapeutic guidelines.

Keywords: Atypical antipsychotics (AAP), peripheral effects, inflammatory response, endocrine response, micro biome

Introduction

Sixty-eight years ago, when chlorpromazine's sedative effects on psychotic patients were discovered, antipsychotics became widely utilised in clinical psychiatry and neuroscience research patients [1]. Antipsychotic medications are divided into two categories based on the clinical effects they cause: normal and atypical. Antipsychotics of the atypical (AAP) or second-generation (SGA) type are helpful in treating both positive and negative symptoms of schizophrenia, as well as improving cognition in some areas. Compared to traditional antipsychotics, AAP are the first line of treatment for a variety of mental health issues because they induce far fewer EPS and carry a lower risk of

pseudo-parkinsonism and catalepsy. The FDA has approved the use of AAP for other psychiatric conditions, including bipolar disorder, major depressive disorder with psychotic features, acute agitation, Tourette syndrome, borderline personality disorder, dementia and substance-induced psychotic disorder, as well as diagnosed psychiatric conditions in children, despite the fact that they were originally prescribed for psychotic disorders like schizophrenia. Because these medicines have an affinity for a wide range of neurotransmitter receptors found in the central nervous system, peripheral organs, tissues, and cells, there are pharmacological and adverse consequences associated with AAP use. Psychiatric and peripheral effects are generated by each AAP's specific affinity pattern, which acts on dopamine (DA) D1-D2-D3-D4-D5 receptors, as well as adrenergic α -1 and α -2, serotoninergic 5-HT2A and 5-HT2C, and muscarinic receptors. There are negative effects associated with AAP, regardless of how effective they are in treating mental disorders and how low their EPS rate is[2] Well-known side effects of AAP include weight gain, type 2 diabetes, dyslipidemia, and a resulting increase in cardiovascular disease risk factors, such as AAP intake, on the other hand, causes clinically important but often overlooked changes in the immunological and endocrine systems, as well as the micro biome of the intestines. These changes are often ignored. These alterations have a major impact on the onset of chronic inflammatory and metabolic abnormalities, which have an impact on patients' ability to recover and their quality of life. AAP intake alters the circulation levels of many hormones in both humans and animals. Oriexigenic and anorexigenic molecules, as well as hypothalamic and pituitary-secreted hormones, are all impacted. AAP intake alters leukocyte phenotype and cell count in humans and animal models[3]. Well-known side effects of AAP include weight gain, type 2 diabetes, dyslipidemia, and a resulting increase in cardiovascular disease risk factors, such as AAP intake, on the other hand, causes clinically important but often overlooked changes in the immunological and endocrine systems, as well as the micro biome of the intestines. These changes are often ignored. These alterations have a major impact on the onset of chronic inflammatory and metabolic abnormalities, which have an impact on patients' ability to recover and their quality of life. AAP intake alters the circulation levels of many

hormones in both humans and animals. Origexigenic and anorexigenic molecules, as well as hypothalamic and pituitary-secreted hormones, are all impacted. AAP intake alters leukocyte phenotype and cell count in humans and animal models [3]. Macrophage (MQ) activity is linked to the synthesis and release of cytokines, cell death, and the differentiation of (Th1 and Th2), as well as apoptosis and phagocytosis, according to the data. According to these and other reports, AAP can alter peripheral levels of pro-inflammation, anti-inflammation, and growth factor molecules like C-reactive protein, interleukin 1b, interleukin 6, interleukin 12, interleukin 10, tumour necrosis factor 1, interferon-g, and others, affecting the systemic health of an individual[4]. Patients who take AAP may have changes in their hormonal and inflammatory levels as a result. Intestinal micro biome involvement in treatment response is becoming increasingly clear, as evidenced by the expanding body of research. Furthermore, gut bacteria may be required for undesirable consequences like weight gain to occur. AAP have been authorized by the FDA to treat schizophrenia and other psychiatric illnesses. This review summarises clinical and experimental research that have shown immunological, endocrine, and intestinal micro biome alterations caused by ingestion of each AAP[5].

Why Is It Important to Make Evident the Neuroendocrine Effects Induced by AAP Consumption?

For severe psychiatric illnesses such as schizophrenia and schizoaffective disorder maintenance, antipsychotic medication is the primary and foundational treatment [6]. These drugs don't just affect the brain; they also cause hyperphagia, hyperglycemia, dyslipidemia, weight gain, diabetes mellitus, and insulin resistance, all of which can lead to decreased life expectancy, poor patient compliance, and sudden death. The most serious side effect of AAP treatment is the development of hyperphagia. In daily clinical practise, patients' prolonged intake of AAP results in metabolic abnormalities as well as three clinically significant concerns that healthcare practitioners commonly overlook. To begin,

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patients who are treated with AAP have endocrine and immunological effects, which are detailed in the following sections. Second, although being more frequent than previously thought (about 66 percent of psychiatrists use AAPs in combination), the effects of co-treatment with AAP and psychiatric medicine are still being studied [7]. When two or more psychiatric diagnoses are present, the most common reason for co-treatment is that the patient is resistant to treatment with clozapine monotherapy or has been diagnosed with two or more psychiatric diagnoses. The clinician may also have used more than one antipsychotic at the same time while titrating another one (switching medications because of lack of response or a better safety profile). AAP use in conjunction with other drugs like benzodiazepines (adjunctive therapy for acute agitation, comorbid anxiety or distress), antidepressants (as adjunctive therapy in schizophrenia for persistent negative symptoms, comorbid major depressive disorder and suicide risk, APs are also used as adjunctive therapy for treatment-resistant major depressive disorder and major depressive disorder with psychotic features, is the third issue.).Finally AAP have become first-choice medicines for treating schizophrenia and other psychoses because to the decreased chance of developing EPS, as evidenced by their broad therapeutic usage [8]. There are a number of neurotransmitter receptors, such as 5-HT and D, which are expressed in peripheral cell types such as leukocytes and gland cells and are thus very promiscuous in their interaction with these medications. Figure 1 shows that AAP do not act equally, which helps us understand the wide range of effects these medications have on the body as a whole. They have structural heterogeneity, and therapeutic effects, while usually comparable, have particularities described by their diverse physicochemical interactions with a variety of receptors initially (see Table 1). Activation of the heterotrimeric Gprotein (GPCR) is caused by the interactions between these medicines and their receptor, which first produces conformational changes within the receptor structure[9].

There have also been discoveries in the last decade about new mechanisms associated with GPCR function like the ability of b-arrestins to act as multifunctional proteins and activate multiple

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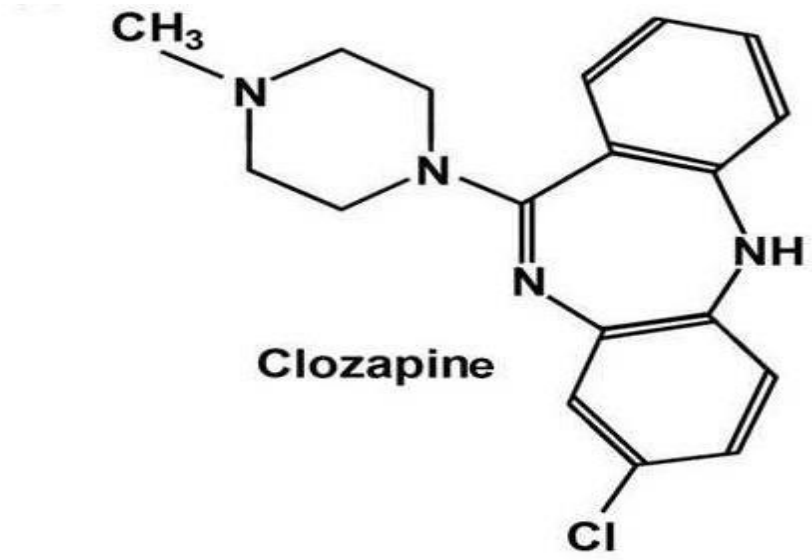
mediators like the proto-oncogene tyrosine-protein kinase SRC, nuclear factor kB, and 3-phosphoinositide kinase. A ligand's ability to preferentially activate G protein-dependent or G protein-dependent signaling is referred to as "biased ago Using this cutting-edge new idea, scientists can better understand how stimulants interact with distinct receptor conformation states and how they can change them. Recent research has also shown that receptor functional selectivity is a dynamic and adaptive process that may be influenced by physiopathological circumstances.



Clozapine

Figure1: Chemical structure of atypical antipsychotic[10]

The combined impact of two or more AAP or poly-pharmacy can also produce a process known as Cellular convergence of signalling pathways in instances such as co-treatment. Signals begun with varying relative intensities of signal can have a varied overall result, and events occurring at the cell membrane can have varying repercussions for the entire cell[11]. AAP users' changes in soluble mediators such cytokines and hormones mirror these events. AAP-Induced Immunoendocrine Peripheral Effects **Clozapine** is the most often prescribed antipsychotics (AAPs) that have been authorized by the Food and Drug Administration (FDA).

Clozapine

Since its FDA approval in 1989 for treatment-resistant schizophrenia following 31 years of research and clinical testing, clozapine has become one of the most effective antipsychotics for the treatment of schizophrenia, psychosis and depression. Yet due to its wide variety of side effects and compliance issues for many patients, it isn't the first-line medication of choice[12]. Because of its potentially harmful and life-threatening adverse effects, such as myocarditis, seizures, agranulocytosis, or granulocytopenia, and gastrointestinal low motility, Clozapine is frequently stopped. It is a 5-HT2A and D4 receptor antagonist. -adrenergic, histaminergic H1, and cholinergic receptors are among the other receptors. As a result, molecular mechanisms of action and medication response predictors cannot be fully understood. Other receptors that this medication blocks include H1, 5-HT2C, and M3, all of which contribute to weight gain and metabolic side effects such as glycemic dysregulation and insulin resistance. Clozapine, which is processed by the liver cytochrome P450 (CYP) system, may interact with a variety of medications. CYP3A4 and 1A2 convert clozapine to nor-clozapine and clozapine N-oxide, respectively, whereas CYP3A4 converts neither into clozapine. Though at therapeutic concentrations of clozapine (24%), the role of CYP2C19 is equally important, it is less so than that of CYP2C9 (12%) and 2D6 (6%).[13]. Then, clozapine blood levels may need to be monitored if inhibitors or inducers of CYP1A2 (such as antifungals, oral contraceptives, fluvoxamine, ciprofloxacin, caffeine, and disulfiram) and both inhibitors and inducers (such as cimetidine, erythromycin, and clarithromycin) of CYP13A4 are used. Tobacco smoking has the potential to alter clozapine metabolism by inducing CYP1A2. Clozapine treatment at dosages of 1–10 mg/kg, 7.5 mg/kg, 10 mg/kg, and 2–20 mg/kg has been shown to cause endocrine changes in animal models. Because of its affinity for M3 receptors, clozapine also raised leptin levels substantially, which have been related to reduced insulin release by b-cells, glucose homeostasis regulation, and increased body weight. Only olanzapine and clozapine have been found to have a high affinity for M3 receptors, according to research. Thus, the overall rise in leptin levels and the link to BMI imply that leptin functions as a negative feedback signal when fat levels rise. In vitro, clozapine has been shown to affect metabolism via the hypothalamus insulin signalling system.

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Clozapine inhibited insulin-induced activation of AKT in neuron cell lines derived from mHypoE-46 and rHypoE-19 donors[14]. Aside from inhibiting 5-HT2AR signalling via G protein-dependent pathways, clozapine is unique among GPCR antagonists in that it also promotes 5-HT2AR internalization and stimulates AKT signalling via a 5-HT2AR-mediated process. When this medication was administered intravenously to Wistar rats in doses ranging from 2.5 mg/kg to 10 mg/kg, the corticosterone and glucagon levels spiked, explaining the development of hyperglycemia.[10].

• Treatment-resistant schizophrenia • Psychosis • Depression	• Glycemic deregulation • Insulin resistance • Increase in leptin levels • Increased cholesterol concentration • Sialorrhea (secondary to VIP interaction with muscarinic receptor) • Ovarian mitochondrial dysfunction	• Increased levels of IL-10, IL-6, and TNF-α • Decreased levels of IL-12 • Reduction in NO levels • Decreased expression of $5\text{-HT}_{2A/2C}$ in T lymphocytes • Inhibits Th1 differentiation

TABLE 1: Immunoendocrine peripheral effects induced by Clozapine

Clozapine enhanced IL-10 production and reduced IL-12 secretion in MQs after 5 days of incubation and when stimulated with lipopolysaccharide (LPS) for 24 hours, according to research on its effects on MQs. Clozapine (10–100M) also decreased the generation of nitric oxide (NO) and IL-12p40 by LPS-stimulated BMDM in female C57BL/6 mice. Similar effects to those mentioned above in cell cultures have been seen in MQs in investigations conducted in animal models. Clozapine administration increased IL-6 and TNF-a with sex-specific changes in a perinatal phencyclidine rat model, which can fit in the theory of the "cytokine signature" seen in blood leukocytes from healthy volunteers incubated with clozapine (1M) and fit in with the "cytokine signature" theory. Clozapine (45 mg/kg/day) caused myocarditis in Wistar rats, which was linked to lymphocytic infiltrates and resulted in the production of ROS, cytokines, and TNF-a. The daily administration of the

antipsychotic drug clozapine(10 mg/kg) substantially decreased IL-1b, TNF-a, and IL-2 levels in 90-day-old Wistar rats prenatally treated with LPS. Clozapine intake alters the profile of circulating cytokines, thus which should be taken into account as well. There were nine patients with schizophrenia or schizoaffective disorder treated with clozapine 100–400 mg/day who developed fever after the initial intake, and IL-6 may play an important role in the interaction effect between the length of therapy and the development of fever [15]. It's also been proven that clozapine raises the levels of the IL-2 receptor soluble (sIL-2R) as well as IL-6. Adipokine resistin, on the other hand, has been linked to a variety of acute and chronic inflammatory conditions, as well as promoting human mononuclear cell production of TNF-a and IL-6 (see **Table 2**).

Conclusion

The bidirectional communication between the SNC with other peripheral systems occurs by the release of soluble molecules that interact with their receptors. Any cell in the organism that bears a functional receptor for a molecule will respond when they interact. The complex structure that confers pharmacological on-specificity to AAPs allows for the interaction with the receptors they have an affinity for, not only in the CNS but also in all body cells. This result leads to the therapeutic effect of AAPs in various psychiatric conditions and their possible ability to modify he endocrine and immune systems as well as the gut microbiota. The therapeutic effect of AAPs is exhibited by the antagonismin CNS receptors that are involved in the pathophysiology ofthe disease. In schizophrenia, for example, the positive and negative symptoms decrease due to the AAP-receptor interaction in the mesocortical and mesolimbic pathways, although HPRL is caused by the antagonism of receptors in the tuberoinfundibular pathway. In addition, the antagonism of neurotransmitter receptors on leukocytes and glandular cells has immune and endocrine effects. The effect of each AAP is unique and depends on specificity and affinity characteristics. AAPs are drugs prescribed for various psychiatric conditions due to their high efficiency and low rate of extrapyramidal effects. However, these drugs have systemic effects that are not only metabolic but

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also related to changes in endocrine and immune responses. Having greater knowledge of these immune, endocrine, and microbiota effects, allows clinicians to have a broader point of view and more significant criteria to prescribe these drugs to patients, considering that the adverse effects can modify the systemic response and generate undesirable effects, with a direct impact on the patients' quality of life. It is necessary to start a new generation of drugs that support the resolution of psychiatric symptoms with higher specificity to prevent acute adverse effects and the patients' systemic deterioration by chronic consumption.

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