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Medical Education

The story of antipsychotics: A metaphorical overview

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Metaphors serve as a vital tool for learners since they not only provide the learners with a source of inspiration and motivation, but also help them conceptualize new knowledge [1]. "The essence of metaphors lies in understanding and experiencing one kind of thing in terms of another" [2]. Metaphors can serve as a constructive as well as a reinforcing educational aid. They can do so by creating an understanding of complex processes and by reinforcing known concepts while linking them with something familiar [3].

The practice of using metaphors in the medical sphere dates back to the 19th and early 20th centuries. It all began years back when there was a lack of diagnostic aids and metaphors served as the only beacon of light to understand medical images of clinical signs and pathology. Rice water stools in cholera and grape-like vesicles seen in hydatidiform mole are common examples of metaphorical usage [4]. The current generation of physicians possess only a dim idea of the use of metaphors in clinical discourse. By being cognizant about the appropriate use of metaphorical language, they can explain the patients about their medical condition in an easier and comprehensible manner [5]. Moreover, metaphors can serve as a useful tool for medical education.

Psychosis is a syndrome consisting of an amalgamation of various symptoms in which a person's mental capacity, effective response, and capacity to recognize reality, communicate, and relate to others is impaired. Schizophrenia is the most common and best known psychotic illness and is characterized by a combination of psychotic symptoms such as hallucinations, delusions, disorganization, and cognitive dysfunctions [6]. There are various hypotheses explaining the pathophysiology of schizophrenia. Dopamine and glutamate hypothesis are the most well accepted of these.

Dopamine hypothesis is laid on the foundation that symptoms of schizophrenia result from excess dopaminergic transmission especially in the mesolimbic and striatal regions of the brain which ultimately lead to the manifestation of positive symptoms of schizophrenia such as delusions and hallucinations. Hyperactivity of the mesolimbic dopamine pathway causes positive symptoms of psychosis while hypoactivity of mesocortical dopamine pathway is responsible for the negative symptoms. The administration of a D2 receptor antagonist blocks the binding of dopamine to D2 receptor and helps reduce the hyperactivity of dopaminergic pathway, but at the same time decreases the dopamine levels further in the mesocortical pathway, leading to side effects such as psychomotor slowing, emotional quieting, and affective indifference. Glutamate hypothesis revolves around the fact that NMDA receptor hypofunctioning prevents glutamate from exerting its full action and thereby prevents release of gamma-aminobutyric acid (GABA) from the interneuron. This leads to disinhibition and excessive release of glutamate downstream which is responsible for excessive stimulation of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens [7].

Typical antipsychotics (dopamine antagonists) were the first group of drugs used to treat psychosis. A landmark change in the field of antipsychotic medications was seen with the advent of the atypical antipsychotics. The different categories of atypical antipsychotics include: serotonin/dopamine antagonists, multi-acting receptor targeted agents and dopamine partial agonists. It is important to discuss the reason for which these different categories of antipsychotics were unfolded.

Researchers had been suggesting that in addition to dopamine, modulating the levels of another neurotransmitter, serotonin could be helpful in the treatment of schizophrenia. It was then realized that $5HT_{2A}$ stimulation of cortical pyramidal neurons by serotonin led to a block in the downstream release of dopamine in the striatum through stimulation of glutamate release in the brainstem that triggered inhibitory GABA, thereby inhibiting dopamine release. Hence, if serotonin is blocked, dopamine will be released in striatum, where

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decreased dopamine levels were responsible for the extrapyramidal symptoms. Moreover, negative symptoms which occur due to the decreased levels of dopamine in the mesocortical pathway could also be resolved by blocking serotonin. Atypical antipsychotics were introduced in line with this concept. Atypical antipsychotics with a higher selectivity for $5HT_{2A}$ receptors and dopamine D2 receptors were labeled as Serotonin/Dopamine antagonists. Drugs showing an affinity for $5HT_{2A}$, D_2, and other receptors (such as histaminergic and $5HT_{1A)}$ were classified as multi-acting receptor targeted antipsychotic. They possess $5HT_{1A}$ partial agonistic actions in addition to their $5HT_{2A}$ and Dopamine (D2) receptor antagonism. Postsynaptic $5HT_{1A}$ receptors in the prefrontal cortex have a role in accelerating dopamine release in the striatum. In addition, presynaptic $5HT_{1A}$ receptor stimulation in raphe causes lack of serotonin release thereby allowing dopamine release in the striatum. Dopamine agonists (DPAs) were introduced on account of their partial agonist property which enables them to bind to the dopamine receptor in an intermediary manner. They help to produce the right balance between full agonism and complete antagonism with antipsychotic actions but without extrapyramidal symptoms. In regard to the glutaminergic hypothesis, research is still ongoing on new glutaminergic modulating agents that can be used for the treatment of Schizophrenia. Agents acting on metabotropic glutamate receptors (mGluRs) and AMPA receptor modulators are examples of new glutaminergic modulating agents which can constitute future treatment of Schizophrenia [8,9].

The varied number of typical and atypical antipsychotics that are available today are a testimony to the evolutionary change in the treatment of psychosis. Here, we will discuss the unique characteristics, indications, and adverse effects of antipsychotics using a metaphorical outlook.

There was once a forest which was inhabited by two groups of allies. One group was that of the veteran typical antipsychotics, while the other group was that of the young atypical antipsychotics. Unlike the veterans who believed in living together as one joint family, members of the atypical ally followed the new generation ideals of living in a nuclear family. Hence, the atypicals decided to divide themselves into three subgroups, i.e., pines, dones, and DPAs. The typical antipsychotic group comprised of various members such as chlorpromazine, haloperidol, fluphenazine, trifluoperazine, loxapine, thiothixene, and perphenazine. Among the atypical antipsyhotics group, the pines (multi-acting receptor targeted agents) included asenapine, clozapine, olanzapine, quetiapine, the dones (serotonin/dopamine antagonists) included iloperidone, lurasidone, paliperidone, risperidone, ziprasidone, and the DPAs included aripiprazole, brexpiprazole, and cariprazine [7].

Once upon a time on a bright sunny morning, a tribal population of the members of the human race invaded the forest with a motive to hold the antipsychotic allies captive. Both groups seemed to be frightened of the tribe and tried to defend themselves by boasting their special qualities. Typical antipsychotics took the initiative and said, "Our oldest member Chlorpromazine is here since 1952, and we have been rendering help to the human race by modulating the activity of Dopamine" [8,10]. To this, the tribe questioned, "How do you modulate dopamine's activity?" Typicals smiled and answered, "We do this by blocking D2 receptors". As we already know, the excessive release of Dopamine in mesolimbic pathway is responsible for positive symptoms of Schizophrenia. Hence, by decreasing the effect of dopamine, we help to relieve psychotic symptoms [10].

Now, the atypical antipsychotics felt the need to speak up and defend themselves. Atypicals shouted out, "Our group of atypical antipsychotics has varied members that not only exert blockade of D2 receptors but can also have an effect on 5HT receptors. Due to our effect on 5HT receptors, we exert negligible extrapyramidal side effects, unlike the typical antipsychotics which can lead to tardive dyskinesia and Parkinson's disease. To add to this, we help to reduce the positive as well as negative symptoms of schizophrenia. Moreover, members of our DPA subgroup are distinctive due to their partial dopamine (D2 receptor) agonistic action. On account of the unique properties stated, we are commonly referred to as Atypicals" [10,11].

The tribe looked confused and asked, "D2 agonism? However, don't psychotic patients already have increased Dopamine levels?" DPA subgroup from the family of atypical antipsychotics replied, "Yes, but by acting as partial D2 agonists, we do not allow the full D2 agonists to act." The veteran typicals tried to create a debate by stating, "Well, it is important to be aware that Clozapine and Olanzapine pose the highest metabolic risk to patients and to add to this, Clozapine also requires blood count monitoring." Atypicals defended, "Well, you must know that In spite of causing weight gain and agranulocytosis, Clozapine is the only ray of hope in refractory psychosis" [10,11].

Then typicals winked and proudly quoted "Our member Haloperidol is highly potent and causes limited anticholinergic side effects, unlike the atypicals. Moreover, Haloperidol is here since 1958, while the atypicals came only in 1990s" [8,10]. This was followed by a comment from the atypicals, "Unlike the typical antipsychotics, few of our members can be used not only in schizophrenia but also in Bipolar disorder (Quetiapine, Risperidone) and autism (Aripiprazole and Risperidone). In fact, Aripiprazole is the first line agent in Tourette disorder. Additionally, Lurasidone, Olanzapine, and Quetiapine can be used in Bipolar disorder, while Aripiprazole and Brexpiprazole can be used in Unipolar depression" [10].

The tribe seemed interested and said, "Oh, atypical antipsyhcotics seem quite unique and advantageous to our human race." In response to this, the typicals spoke up, "True! But do you know that the benefits shown by atypicals are not devoid of risks? I will tell you about some of the side effects associated with them. Iloperidone requires monitored dose titration due to its ability to cause orthostasis. Olanzapine has the highest placental passage and poses more neonatal risks compared to other antipsyhcotics. Paliperidone, risperidone, and amisulpride have shown to be associated with hyperprolactinemia while Quetiapine and Clozapine pose an increased risk of sedation. Moreover, the use of sertindole is restricted on account of the risk of cardiac arrhythmias (OTc prolongation) that can occur with its use." The atypicals looked with awe and said

"Few members of our group (Paliperidone, Risperidone, and Aripiprazole) are available as long-acting injectables. Does your typical antipsychotic group have any injectables?" The typicals replied "Of course we do! Haloperidol and Fluphenazine are available as injectables" [10].

The tribe seemed convinced by both groups and said, "Typical and atypical antipsychotics, both groups have been of immense help to humans, and we hope that you all live together in harmony. We do not want to invade your territory and request you to extend your support to humans even in the coming future." The typical and atypical antipsychotics looked at each other and smiled, while the tribe left in search for a new abode.

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Conflicts of interest

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