Pathophysiology of Antipsychotic Drug–Induced Movement Disorders

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Explaining the underlying mechanisms of antipsychotic drug–induced movement disorders remains a substantial challenge. The association of atypical antipsychotic agents with fewer drug-induced movement disorders than conventional agents has engendered several pathophysiologic hypotheses: (1) the hypothesis that, unlike conventional antipsychotic agents, atypical antipsychotics have greater activity in blocking serotonin-2A ($5\text{-}HT_{2A}$) receptors than dopamine-2 (D_2) receptors, which mitigates extrapyramidal symptoms; (2) the hypothesis that atypical antipsychotics block D_2 receptors only long enough to cause an antipsychotic action, but not as long as conventional agents; (3) the hypothesis that, in tardive dyskinesia, the nigrostriatal dopamine receptor system might develop increased sensitivity to dopamine as a result of treatment with conventional antipsychotic drugs, but this may not occur with atypical antipsychotics; and (4) the hypothesis that there might be a genetic association in tardive dystonia relating to the dopamine D_3 allele. A number of factors contribute to the difficult task of gaining insight into the pathophysiologic processes of antipsychotic agents and why these agents may lead to drug-induced movement disorders.

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Despite an extensive research base for understanding the mechanisms of action of antipsychotic agents, the specific pathophysiologic processes underlying movement disorders remain incompletely understood. Compared with conventional antipsychotics, atypical antipsychotics have substantially decreased the incidence and severity of drug-induced movement disorders, such as the acute extrapyramidal symptoms (EPS) and tardive dyskinesia.[1] These observations have engendered a variety of hypotheses to explain the underlying pathophysiologic processes in a comprehensive explanation of how these agents differ in regard to their impact on patient, drug, and temporal factors. Fortunately, as the understanding of movement disorders evolves and new drug development advances, researchers and physicians may have the opportunity to witness the resolution of these iatrogenic problems.

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CHALLENGES TO DEVELOPING EXPLANATORY MODELS

Many factors contribute to the difficulty of gaining insight into the pathophysiologic processes of antipsychotic side effects and why some of these agents may lead to more drug-induced movement disorders than do other drugs. First, each drug-induced movement disorder has unique features and neural anatomical constructs. For example, although the pathophysiology of dystonia and parkinsonism is generally well understood, the pathophysiology of akathisia remains enigmatic. Despite the classification of these 3 movement disorders as acute EPS, the differences among these unique disorders contribute to the challenge of formulating a clear, specific understanding of each one individually. Also, researching each disorder independently is difficult because patients often experience more than one movement disorder simultaneously. When patients have comorbid movement disorders, it is difficult to gather information on each disorder to the exclusion of the others.

A scarcity of patients who have never been exposed to typical neuroleptic medications exists. This scarcity creates a sample limitation that skews estimates of the prevalence of spontaneous dyskinesias resulting from psychiatric illness rather than from antipsychotic treatment. Therefore, it is difficult to adequately assess the relationship between current and past antipsychotic treatment and motor side effects.

Another factor contributing to the formidable task of investigating the etiology of movement disorders is the like-

lihood that some patients have a unique vulnerability for developing EPS or tardive dyskinesia. For example, the patient-related factors of both gender and age can affect the probability that an individual will develop a drug-induced movement disorder. Young men are most susceptible to dystonic reactions,[2] whereas elderly men and women appear to be more vulnerable than young men and women to the parkinsonian features induced by either atypical or conventional antipsychotics.[3] Drug-induced tardive dyskinesia often appears early in the course of treatment in elderly patients and is 5 to 6 times more likely to occur in older than younger patients.[4] The majority of studies indicate that elderly women are more vulnerable to tardive dyskinesia, but some conflicting data indicate equal vulnerability for both genders.[4–6]

Additionally, time is another factor that must be considered in understanding the pathophysiology of movement disorders. Akathisia can develop within a few minutes to a few hours after ingesting an antipsychotic, yet dystonia usually does not occur until 12 hours or more after an antipsychotic has been consumed. Indeed, the majority of dystonic reactions occur in the 24- to 48-hour period after the first antipsychotic dose.[6] Alternatively, parkinsonian features often do not develop until several days after the first antipsychotic dose.[6] Researchers have not yet come to a sufficient explanation for these differences, and these variations can complicate research methods and outcomes.

A final challenge in developing a model of movement disorders is that both preclinical and clinical knowledge has evolved along similar time frames. Although many preclinical models[5–7] have been created to identify the underlying pathophysiologic processes of tardive dyskinesia, no one model has offered a parsimonious explanation for what happens clinically. All of these factors that influence research difficulties exist in the context of variations among the antipsychotic drugs and their relative propensities to induce these movement disorders.

CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS AND ADVERSE EVENTS

Traditionally, EPS with antipsychotic use were primarily associated with milligram potency of the conventional agents. However, this distinction does not apply to the atypical antipsychotics as evidenced by the lower rates of EPS when these drugs are used within the recommended therapeutic dose ranges.[1] A recent addition to the pharmacopeia is the dopamine partial agonist aripiprazole. When this drug is used at recommended doses, it also has low rates of EPS,[8] although drug-induced akathisia manifests in some patients.

The dopamine receptor blockade hypothesis dominated the conceptual underpinnings of drug-induced movement disorders for many years. Early explanations for drug-induced movement disorders with conventional antipsychotics were specifically related to dopamine receptor blockade. This hypothesis proposes that after antipsychotics are ingested and delivered throughout the central nervous system, D_2 receptors in all 4 dopamine pathways might be simultaneously blocked, resulting in various adverse events. The consensus has been that if approximately 80% of the dopamine receptors in the nigrostriatal pathway are blocked, then patients are likely to develop a drug-induced movement disorder.[6]

The association of atypical antipsychotic agents with fewer drug-induced EPS and other adverse events than conventional agents has engendered new theories on the relationship between the mechanisms of action of antipsychotics and their tendency to cause movement disorders.

PATHOPHYSIOLOGIC HYPOTHESES

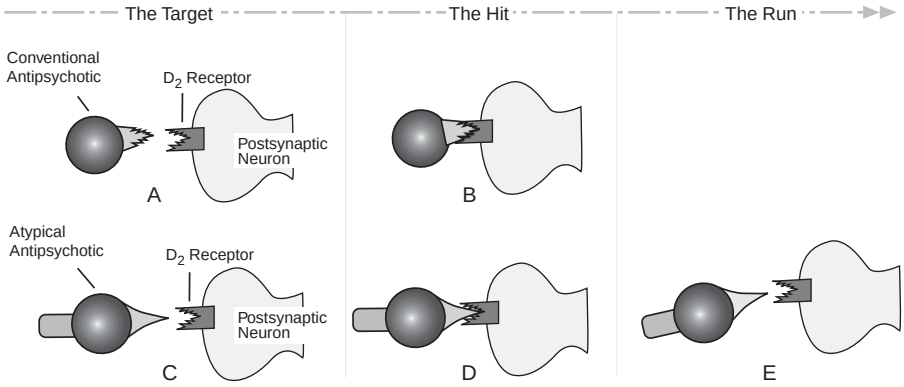
Blocking Serotonin

One popular hypothesis has been that, unlike conventional antipsychotic agents, atypical antipsychotics block serotonin-2A ($5\text{-}HT_{2A}$) receptors in addition to D_2 receptors.[1,9] Serotonin is thought to have an important influence on dopamine in that it inhibits dopamine release from dopaminergic axon terminals in varying degrees from one pathway to another. Therefore, researchers have speculated that blocking $5\text{-}HT_{2A}$ receptors in these pathways would increase the release of dopamine. According to this theory, when $5\text{-}HT_{2A}$ receptors are blocked in the prefrontal cortical, mesolimbic, nigrostriatal, and tuberoinfundibular pathways, dopamine may be released to such an extent that some of the D_2 blockade of the antipsychotic is reversed, thereby reducing some harmful adverse effects such as EPS and cognitive impairment. It has been speculated that antagonism of serotonin in the mesolimbic pathway was not robust enough to cause the reversal of D_2 receptor blockade or mitigate the actions of atypical antipsychotics on the positive symptoms of psychosis.[6]

However, this theory was challenged when subsequent research[10] revealed that the threshold occupancy of D_2 for antipsychotic efficacy (in the mesolimbic dopamine pathway) appeared to be approximately 65%, and the threshold occupancy of D_2 for precipitating EPS (in the nigrostriatal pathway) about 80% for both atypical and conventional antipsychotics. Additionally, the atypical agents block more than 90% of the $5\text{-}HT_{2A}$ receptors at low doses that are not efficacious, and these drugs do not block 80% or more of the D_2 receptors at efficacious doses.[9] Therefore, whether $5\text{-}HT_{2A}$ receptors were blocked or not, it is debatable whether the atypical agents caused fewer EPS because of lower D_2 occupancy. Indeed, it may be that the $5\text{-}HT_{2A}$ antagonist effects in the prefrontal cortical and mesolimbic regions have antipsychotic efficacy that supplements the D_2 antagonism. These effects would allow for lower atypical antipsychotic doses, which do not block more than 80% of the nigrostriatal D_2 receptors and thus would not cause EPS.

Figure 1. Conventional vs. Atypical Antipsychotic Mechanisms[a]

Conventional: Because of the biochemical properties of conventional antipsychotics, their binding to postsynaptic dopamine D_2 receptors is tight and long lasting, as shown by the teeth on the binding site of the conventional antipsychotic (A). The D_2 receptor on the right has grooves where the teeth of the drug can bind tightly, locking the drug into the receptor binding site (B) to block it in a long-lasting manner.



Atypical: The biochemical nature of binding for atypical antipsychotics to postsynaptic D_2 receptors is loose, as shown by its smooth binding site, which does not fit well into the grooves of the receptor (C). *The Hit:* Note that the drug fits loosely into the D_2 receptor without getting locked into its grooves (D), unlike conventional antipsychotics. *The Run:* Because an atypical antipsychotic fits loosely into the D_2 receptor, it slips off easily after binding only briefly, then runs away (E). This process is called rapid dissociation.

[a]Reprinted with permission from Stahl.[12]

Rapid Dissociation

The process of rapid dissociation is a new hypothesis to identify the general difference between conventional and atypical antipsychotics as well as account for differences in side effect profiles among the atypical antipsychotics.[11] It speculates that atypical antipsychotics are atypical because they block D_2 receptors only long enough to cause antipsychotic action, but not long enough to cause EPS and other harmful adverse events (Figure 1).[12] This hypothesis is supported by evidence that rapid dissociation from the D_2 receptor is correlated with low EPS potential.[13] Rapid dissociation from the D_2 receptors seems to occur more readily with an agent that has low potency (i.e., agent that requires higher milligram doses such as clozapine) as opposed to high potency (i.e., agent that requires lower milligram doses such as risperidone). This process appears to not only correlate roughly with the tendency for atypical agents to cause different adverse motor system effects within the class but also differentiates atypical from conventional antipsychotics.

However, this theory is difficult to prove or disprove. The duration of the D_2 receptor blockade is highly correlated with milligram potency. Since most of the atypical antipsychotics are effective for patients at levels below the 80% dopamine receptor occupancy in the nigrostriatum, the simple explanation for whether a patient will develop acute EPS remains based on the threshold for dopamine receptor blockade in these competing hypotheses. Additionally, all atypical antipsychotics when given in high doses are capable of precipitating EPS. In fact, clozapine has been reported to induce akathisia,[14] although dystonic and parkinsonian features rarely occur at any dose with clozapine for the vast majority of patients.

Dopamine Receptor Hypersensitivity in Tardive Dyskinesia

Several pathophysiologic hypotheses have been proposed to explain tardive dyskinesia, a movement disorder that occurs over time, rather than in the acute phase of treatment. The most popular theory, which has dominated the conceptual underpinnings of research since the early 1970s, focuses on dopamine receptor hypersensitivity. This hypothesis proposes that the nigrostriatal dopamine receptor system develops increased sensitivity to dopamine as a consequence of chronic blockade resulting from conventional atypical antipsychotic drugs.[15,16] A majority of what has been widely accepted as substantiating evidence for the dopamine hypersensitivity hypothesis has been derived from rodent models. In rodents, research has shown an increase in behavioral responses to dopamine agonists following dopamine antagonist treatment of a single dose as well as after treatment lasting a few days, several weeks, and 1 year.[5] Additionally, the neurochemical change of an increase in the number of dopamine D_2 receptors in animals correlates with behavioral changes in most studies.[5,17]

However, although clinical data suggest that dopamine antagonism does play a substantial role in the pathophysiology of tardive dyskinesia, no direct data in humans support the dopamine receptor hypersensitivity hypothesis. Many of the observations from animal studies are compatible with the essential clinical aspects of human tardive

dyskinesia: late onset, symptoms without agonist provocation, individual vulnerability, and a potentially irreversible course (changes in animals are reversible within days to weeks of discontinuing treatment). Additionally, postmortem studies have been unable to find substantial differences in D_1 or D_2 receptors in patients.[18]

Dopamine D_3 Allele in Tardive Dystonia

A more recent hypothesis regarding the pathophysiology of tardive dystonia postulated that there might be a genetic association in its development relating to the dopamine D_3 allele. This hypothesis was investigated in a recent study by Mihara et al.,[19] who examined the relationship between tardive dystonia and several genetic factors such as polymorphism of cytochrome P450 2D6 and receptor polymorphisms of dopamine D_2 (TaqI A and -141C Ins/Del polymorphisms) and D_3 (Ser(9)Gly polymorphism). However, after researchers genotyped 9 patients with tardive dystonia for these genetic polymorphisms, they found that no specific genotypes or alleles were overpresented in the patients. This study suggested that these polymorphisms were in fact not related to the development of tardive dystonia.

CONCLUSION

Research into the underlying mechanisms of antipsychotic drug–induced movement disorders has greatly increased our understanding of these disorders as well as enhanced our knowledge about the actions of antipsychotic drugs in several areas of the brain. However, a single explanation of the varied acute EPS and late-onset tardive dyskinesia has not been elucidated. Ultimately, it may be that multiple mechanisms of actions of these drugs account for different movement disorders.

However, the rate and severity of acute EPS and tardive dyskinesia have greatly decreased with the advent of new atypical antipsychotic agents.[1] Additionally, researchers continue to gain insight into the pathophysiology of drug-induced movement disorders by studying schizophrenia, and further advancements in the understanding of schizophrenia have been achieved through progress in understanding the pathophysiology of movement disorders.

This is a fascinating time in neuropsychiatry. We have had the rare opportunity to see not only the onset of drug-induced disorders associated with a major breakthrough in treatment (the conventional agents in the 1950s), but also what appears to be the near resolution of this problem with the current advancements in atypical antipsychotic drugs.

Drug names: aripiprazole (Abilify), clozapine (Clozaril and others), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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