Aripiprazole: Does Partial Dopaminergic Agonism Translate into Clinical Benefits?

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Although the exact biological mechanisms involved in schizophrenia remain unknown, it is widely accepted that monoamine neurotransmitters (e.g., dopamine) play a key role in the symptomatology and pathophysiology of the disease. Since the discovery that the efficacy of phenothiazines was associated with blocking dopaminergic receptors, dopaminergic circuitry of the brain has been a focus of drug development for the treatment of schizophrenia. It became apparent that the traditional antipsychotics had limitations with regard to their ability to improve symptoms of schizophrenia, and they had significant neurologic adverse effects. These findings led to efforts to develop antipsychotics with more optimal therapeutic profiles. Clozapine provided an agent with improved efficacy and negligible extrapyramidal side effects. However, its low but significant risk of agranulocytosis relegated clozapine to a role as the treatment of choice for persons who had demonstrated inadequate response to other agents. This was followed by the development of a series of second-generation antipsychotics (SGAs, i.e., atypical antipsychotics), such as olanzapine and risperidone, in an attempt to discover a “clozapine” without blood dyscrasias. None of these post-clozapine SGAs have yet been proven to be as efficacious as clozapine in treatment-resistant patients or to have the same degree of effects on decreasing suicidality. However, all have demonstrated, to varying degrees, enhanced efficacy for negative symptoms and cognition and improved tolerability compared with typical agents.

Although the exact mechanism of atypicality is uncertain and open to debate, a common hypothesis is that atypical antipsychotics produce less, but adequate, dopaminergic blockade at the dopamine$_{2}$ (D$_{2}$) receptor while producing antagonism at the serotonin$_{2A}$ (5-HT$_{2A}$) receptor. Thus, the relative balance between 5-HT$_{2A}$ antagonism and D$_{2}$ antagonism has been offered as a mechanism for the atypical profile of SGAs. However, lower D$_{2}$ binding or more rapid dissociation from the D$_{2}$ receptor has been proposed as an alternative explanation. Regardless, because of improved tolerability and decreased adverse effects, the atypical antipsychotics are now considered first-line therapy for schizophrenia, at least in North America.

The recent approval of aripiprazole presents practitioners with a new option for the treatment of schizophrenia. Considered a partial dopaminergic agonist, aripiprazole acts on both postsynaptic D$_{2}$ receptors and presynaptic autoreceptors. At the postsynaptic receptor, aripiprazole acts as a functional dopaminergic antagonist at high, but not low, concentrations of dopamine. Because the drug has intrinsic activity, complete blockade of dopaminergic activity does not occur. Instead, dopaminergic-mediated neurotransmission is maintained, although at a less intensive magnitude. This is theoretically attractive, as dopaminergic hypoactivity in the prefrontal cortex is thought to be associated with negative symptoms and cognitive dysfunction in schizophrenia. Aripiprazole’s activity as a partial agonist at dopaminergic autoreceptors is believed to reduce the tendency for up-regulation, which is hypothesized as being a factor contributing not only to the symptomatology...
of schizophrenia, but also to the development of extrapyramidal symptoms and tardive dyskinesia. Thus, aripiprazole, by virtue of its intrinsic dopaminergic activity (partial agonism) seems to differ significantly from other marketed antipsychotic agents, but, as noted below, the clinical significance of this effect is not yet clear.\(^6\)\(^-\)\(^12\) In this regard, the Food and Drug Administration approval process requires superiority compared with placebo and haloperidol. Clinical studies to demonstrate unique properties or superiority of aripiprazole over other SGAs are a secondary consideration until this first hurdle has been crossed.

Available efficacy data have not shown any unique clinical advantages for aripiprazole in schizophrenia. In studies comparing aripiprazole with placebo, haloperidol, and risperidone, results indicate aripiprazole to be significantly more efficacious than placebo and comparable to risperidone and haloperidol.\(^13\)\(^-\)\(^16\) Head-to-head studies of aripiprazole with various SGAs are necessary to make conclusions regarding the relative efficacy of these agents. Clinical trials are needed examining the effects of aripiprazole in suicidal and treatment-refractory patients. Long-term effectiveness studies are also necessary, particularly those examining relative effects of aripiprazole and different SGAs on disease progression, function, quality of life, and use of health services.

Safety and tolerability data indicate that aripiprazole may have some advantages as compared with other SGAs. It appears to have little effect on QTc interval, as well as serum lipid, glucose, or prolactin levels.\(^13\)\(^-\)\(^16\) Weight gain appears to be comparable to that with haloperidol and at the low end of the spectrum of SGAs. In the study comparing cognitive effects of aripiprazole and olanzapine, significantly more weight gain occurred with the latter compound.\(^37\) Use of aripiprazole in the general population and future studies will further define the clinical significance of these metabolic differences from those of other antipsychotics. It must be stressed that uncommon adverse effects are usually not identified until thousands of patients have been treated with a drug. Therefore, until a new drug has had widespread use in general clinical practice, it cannot be assumed that it is free of rare but very serious adverse effects.

As with many newly approved medications, the potential advantages of aripiprazole are yet to be determined. Whether aripiprazole’s different effect on dopaminergic neurons is translated into significant clinical advantages is not yet apparent. Available data do not suggest any superiority with regard to efficacy in short-term trials. However, schizophrenia is a long-term illness, and the true test of the value of new medications is in the maintenance phase of the illness. If aripiprazole’s favorable adverse effect profile passes the test of broad clinical exposure, then it may have significant benefits compared with existing SGAs. Its long elimination half-life (75 h) enables once-daily dosing. As with risperidone and olanzapine, once-daily dosing is a positive factor with regard to patient adherence.\(^18\) No information currently exists regarding aripiprazole’s efficacy in treatment-resistant schizophrenia.

One of the real dangers of a new medication being the sixth agent in a therapeutic category is the possibility that clinicians will primarily use it in patients who have failed treatment with multiple other agents. If this is the case with aripiprazole, we run the risk of clinicians developing an impression that aripiprazole is not effective, because patients who have failed on different agents are less likely to improve with any treatment. This would be an unfortunate occurrence if aripiprazole’s suggested adverse effect advantages are confirmed in general clinical use. Clinicians are encouraged to use it in a variety of patients with schizophrenia so that more accurate clinical impressions can be developed. Furthermore, additional research is necessary before judgments can be made regarding potential advantages of aripiprazole relative to other atypical agents. It is also an open question as to what degree the impairments characteristic of schizophrenia can be remedied with medications acting on the dopamine system. There is suggestive evidence that drugs affecting glutamatergic neurotransmission may be helpful for the illness. Unfortunately, there is also evidence for brain damage in schizophrenia that may not be reversible once it has occurred, requiring a strategy of prevention rather than amelioration.

Initial experience suggests that aripiprazole is being priced in the middle of the range among newer antipsychotics, all of which are far more expensive than older antipsychotics. Given the growing popularity of the SGAs and the limited resources often available for public mental health care, this creates a challenging scenario for healthcare policy decision-makers who, with a finite budget, are attempting to provide services to as many people as possible. In an ideal world, antipsychotics with similar efficacy to safety ratios would be considered equivalent alternatives for first-line use by prescribers. However, price considerations in many healthcare organizations cause pharmacy and therapeutics committees to consider preferred agents within a therapeutic category based upon drug acquisition cost. This process could complicate the tendency to reserve treatment with the newest drugs for patients who have already failed treatment with several others within the class. Although group data suggest that the newer antipsychotics have similar mean efficacy response rates, one cannot reliably predict which patient will respond best to a particular antipsychotic medication. Additionally, the newer antipsychotics vary significantly in their adverse effect profiles. It would be unfortunate if aripiprazole is initially used only in patients who have failed to respond to other SGAs, as use in a self-selected, treatment-resistant population would present us with a biased picture of aripiprazole’s effectiveness and role in treatment. In their formulary decisions, healthcare decision-makers should make arrangements for new drugs, such as aripiprazole, to be used as first-line agents, so that a more accurate assessment of the new drug’s role in treatment can be achieved.

Does partial dopaminergic agonism translate into clinical benefits? Currently available research does not answer this question, but does suggest potential advantages in the adverse effect profile as compared with at least some of the
other SGAs. Head-to-head research comparisons with other SGAs, as well as extensive experience in routine clinical practice, are needed to answer this question.

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