Aripiprazole: an appraisal of the translation of complex receptor effects into clinical outcomes

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Aripiprazole possesses a complex pharmacology with both partial agonist and full antagonist effects. The purpose of this article is to critically review, in the light of its unique receptor pharmacology, the current clinical literature on the use of aripiprazole in the treatment of schizophrenia and mood disorders. There is evidence that aripiprazole is an effective and well tolerated antipsychotic in treating schizophrenia. Now, more recent evidence suggests that aripiprazole may have a role in the treatment of mood disorders. The efficacy side-effect profile of aripiprazole is reviewed herein.

Aripiprazole is the newest agent in a class of medications that are now called Second Generation Antipsychotics (SGAs). Its receptor pharmacology differs from other SGAs [1]. Based upon this, there was much earlier discussion as to whether aripiprazole might be realistically considered the first of so-called third generation antipsychotics. For reasons that will become apparent below, thankfully our field resisted this temptation to (further) complicate our nomenclature, although aripiprazole is considered both new and different within the SGAs. Aripiprazole, an antipsychotic of the quinolinone class, has been available in clinical practice in the USA since late in 2003. The studies reviewed herein confirm that aripiprazole is a broadly efficacious antipsychotic medication. Additionally, its side-effect profile thus far appears favorable – particularly in the context of the emergent side effect typology of SGAs. An oral solution of aripiprazole has just become available in the USA and a dissolvable tablet and short-acting intramuscular preparations of aripiprazole are being developed. There has also been an approved extension of the use of aripiprazole in mood disorders. The purpose of this article is to evaluate aripiprazole's role in the context of its unique receptor profile and to examine the extent to which these properties translate into the clinical arena. To facilitate this, the manuscript has been divided into sections, each addressing key aspects of pharmacotherapy with aripiprazole.

Keywords: aripiprazole, mood disorders, schizophrenia

Unique pharmacology of aripiprazole

Kapur and colleagues, in a series of Positron Emission Tomography (PET) neuroimaging studies of antipsychotic receptor binding, have provided informative data pertinent to the receptor profile and adverse effects of SGAs [2,3]. They describe the need to acquire dopamine (D_2) receptor occupancy rates of 60% and above for therapeutic efficacy with first-generation antipsychotics (FGAs), wherein D2 occupancy at 75% results in the emergence of extrapyramidal side effects. Aripiprazole is different in its profile (see below) since it exhibits partial agonist effects at D_2 and serotonin (5HT1a) receptors [1,4]. This is the major difference between aripiprazole and other currently available FGA and SGA antipsychotics (which generally portray a pharmacologic profile of dopamine and/or serotonin receptor antagonism) in that this agent may act to modulate or stabilize dopamine–serotonin systems in the brain [1,4,5]. This is an appealing hypothesis. When a drug binds to a receptor, it can exert no effect (a complete antagonist), a full effect at the receptor (working as an antagonist), or an effect that is intermediate between these two positions – such as a partial agonist. Since partial agonists have intermediate binding (i.e., lower intrinsic activity than an agonist), they are dependant on their competitive environment as to how much they will exert their intrinsic activity at a receptor. Thus, in schizophrenia where there may be an excess of dopamine in the limbic cortex, aripiprazole will work more like an antagonist. Conversely, in the frontal cortex where dopamine may be underexpressed, aripiprazole will work as an agonist. Thus, this capacity to adopt intermediate binding affinity/intrinsic activity is thought to underline the unique pharmacology of aripiprazole and to the notion of this drug as a neuromodulator [6]. Information from a recent PET study of receptor occupancy by aripiprazole in 15 healthy subjects is consistent with its proposed mechanism of action as a partial agonist-neuromodulator of

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the dopamine (and serotonin) system [7]. At a dose of 2-mg/day, aripiprazole occupied 70 to 80% of striatal D2 dopamine receptors. When the dose of aripiprazole was increased to 30 mg/day, D2 dopamine receptor occupancy was estimated at 95%. This profile has also recently been confirmed in a animal PET study with aripiprazole which showed a dissociation between the extremely high D2 binding profile of this drug and the absence of catalepsy in these rats [8]. Such high D2 dopamine receptor binding occurring in the absence of extrapyramidal side effects or prolactin elevation is consistent with aripiprazole's role as a partial agonist at dopamine receptors. Additionally, the partial agonist effect on 5HT1A serotonin receptors is consistent with neuromodulatory effects on the serotonergic system which may support the clinical effect of mood stablization [9]. With respect to its binding affinity to other neuroreceptors, aripiprazole has minimal antagonism at histaminergic, muscarinic, and α-1 adrenergic receptors [1,2].

In terms of its clinical pharmacokinetics, aripiprazole is rapidly absorbed, binds strongly to plasma proteins and has a long half-life of approximately 75 h. It is best administered as a single daily dose, which can be given either with or without meals. The pharmacokenetics of a recently developed oral solution are similar to the tablet formulation [10]. A dissolvable tablet formulation is under development [9]. The short-acting, intramuscular for aripiprazole, which is under development, also possesses an onset of action [11]. Aripiprazole is metabolized by the hepatic microenzyme system and can be influenced by drug-drug interactions and the metabolism of other drugs. There is evidence of modest elevations of plasma concentration of aripiprazole in the presence of agents (e.g., ketoconazole, quinidine) which inhibit the cytochrome P450 (CYP)3 hepatic microenzymes. Drugs which induce these microenzymes (e.g., carbamazepine) may decrease the availability of aripiprazole. Aprpiprazole is also metabolized by the CYP2D6 enzyme system. Accordingly, it may also be necessary to consider decreasing the dose of aripiprazole in patients receiving concomitant medications (e.g., paroxetine) that inhibit CYP2D6 [13]. This particular metabolic pathway has drawn much attention recently, with the clinical launch of pharmacogenomic chip test for detecting poor metabolizers of the CYP2D6 system. Overall current evidence suggests that drug interactions can be accommodated by minimal adjustments in the daily dosage of aripiprazole. The drug-interaction effects of aripiprazole added to either valproic acid or lithium have been studied and have been shown to be safe combination [14], an important consideration given the use of this agent now in mood disorders.

Beyond the 'classic' pharmacology and receptor affinity-based mechanisms of action, there is now intense interest in understanding whether SGAs such as aripiprazole possess unique mechanisms of action that might explain their broader range of efficacy One emerging area of inquiry comes from reports of animal studies suggesting that SGAs may stimulate nerve cell growth ('neurogenesis') and that these medications may positively ameliorate deficits in nerve growth factor and other brain trophins [15]. There is no information yet on aripiprazole's effect in these areas. Nevertheless, the unique receptor profile is the key aspect of this drug and is seen as a new avenue for drug development in schizophrenia [16].

Clinical efficacy in schizophrenia

There is ample evidence to suggest that aripiprazole is an effective antipsychotic medication [9]. The evidence comes from a variety of sources including registration trials, Phase IV maintenance trials, naturalistic trials and head-to-head comparison trials with other SGAs. Examples of findings from representative studies from each of these sources are given below.

Aripiprazole has been shown in several large clinical trials to be effective in the treatment of positive, negative and depressive symptoms in schizophrenia. Kane and colleagues [17] conducted a placebo-controlled 4-week trial of aripiprazole and haloperidol in over 400 patients (n = 414) with a diagnosis of schizophrenia or schizoaffective disorder. Aripiprazole (15-mg/day and 30-mg/day doses) was superior in efficacy to placebo for total, positive, negative, and general psychopathology scores as well as significantly greater improvement in overall functioning. Another placebo-controlled trial of 4-week duration showed comparable efficacy between two doses of aripiprazole (20 mg/day and 30 mg/day) and risperidone (6 mg/day) in just over 400 patients (n = 404) with schizophrenia [18]. The 20 and 30 mg/day doses of aripiprazole were similar in efficacy. Both doses of aripiprazole performed similarly to risperidone. This is a particularly important study because it is a comparison of aripiprazole with a widely used SGA, risperidone. One comment is that the 6-mg dose of risperidone is higher than the current dose in

practice (now averaging just below 4 mg/day). However, it was a reasonable dose of risperidone to choose at the time the study was conducted. Moreover, this dose of risperidone likely maximized the chance of patients in that arm responding to this drug over the 6-week duration of the study. Thus, this study provides important information indicating equiefficacy of aripiprazole with another SGA.

A 26-week study of aripiprazole (15 mg/day) was conducted in patients who were stable. The definition of relapse was impending decompensation which included prior criteria for worsening of psychosis as well as more core measures of relapse such as need for hospitalization and/or emergency of injurious behaviors [19]. Aripiprazole-treated patients showed less relapses than patients receiving placebo. The effect was evident early on in the trial. A 1-year maintenance trial compared 30 mg/day of aripiprazole with 10 mg/day of haloperidol [20]. There was a higher rate of discontinuation in the haloperidol group, with significantly more patients continuing on aripiprazole than haloperidol (52 vs. 44%). Aripiprazole-treated patients did better on total symptoms, positive, and negative symptoms than patients receiving haloperidol. The effect was evident at week 26 and was sustained throughout the duration of the trial.

There is also a large (n = 1600) open-label trial of aripiprazole in community-based practices called the Broad Effectiveness Trial of Aripiprazole trial (BETA) [21]. In this study, patients were randomized (4:1 ratio) to receive aripiprazole or another (clinician's choice) antipsychotic. The mean aripiprazole dose at end point was 19.9 mg/day, with 47% of patients receiving 15 mg/day. Aripiprazole proved comparable to all other treatments in terms of efficacy. On a patient and caregiver measure of preference of medication, aripiprazole was preferred over prior treatments by most patients. The results from the analysis of this large naturalistic study thus shows that aripiprazole is as safe and effective as other antipsychotic drugs in the treatment of patients with schizophrenia. A European counterpart of this naturalistic study is currently in progress. Information was recently presented on up to 5 years of treatment with aripiprazole [22]. The drug was found to have sustained efficacy with a tolerability profile (see later section) comparable with that described in short-term trials. There is also a study that addresses the issue of switching patients from other SGAs onto aripiprazole [23]. In this study, three strategies for switching were evaluated – an abrupt change, a cross taper, and a gradual taper of both drugs. Each was similar in tolerability. Most clinicians choose to overlap drugs and gradually taper down the first drug and gradually increase aripiprazole to a 15-mg/day dose. However, this remains a complex area of inquiry.

Comparative studies of olanzapine & other SGAs

There is limited information on the efficacy and tolerability of aripiprazole compared with other SGAs. The comparative study of aripiprazole and risperidone was described earlier. McQuade and colleagues recently reported on the results of a 26-week trial of aripiprazole versus olanzapine [24]. Aripiprazole and olanzapine showed comparable efficacy on symptoms but greater improvement on verbal memory. Importantly, aripiprazole was much better tolerated than olanzapine. In total, 37% of olanzapine-treated patients had significant weight gain compared with 14% of aripiprazole-treated patients. Fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol and triglycerides were elevated with olanzapine. There is also data on the open-label extension of this study, which shows the same pattern of metabolic differences between these in drugs [25]. There are no reported studies yet comparing aripiprazole with either quetiapine or ziprasidone. In view of the similar adverse-effect profile of both ziprasidone and aripiprazole, a study comparing these two drugs would be informative and timely.

Dosing considerations for aripiprazole

The chosen dose for each SGA is a major consideration. Indeed, in clinical practice we have observed that the dosing patterns with SGAs are dynamic, with olanzapine, quetiapine and ziprasidone surpassing current recommendations while risperidone has declined in dose since its initial regulatory guideline [26]. An interpretation of the registration studies of aripiprazole suggests that doses of aripiprazole between 15- and 30-mg/day are effective for treating schizophrenia. There is to date no evidence that the 30 mg/day dose is superior. In the BETA trial, there was no evidence for a dose-dependent response with aripiprazole [21]. Accordingly, the 15 mg/day dose of aripiprazole is recommended as both the starting and a maintenance dose of aripiprazole. It is unclear whether increasing the dose beyond the current US Food and Drug Administration (FDA)

recommendation of 30 mg/day confers any additional advantage. Nevertheless, clinicians are learning how best to dose this drug in clinical practice. An analysis in 2003 of prescribing practices from New York public mental health system (NY, USA) showed that 11% of patients were receiving high doses of aripiprazole at above 30 mg/day [27]. The dose equivalency of aripiprazole to other SGAs is currently unclear. In a symposium at the 2004 American Psychiatric Association Annual Meeting [28], attendees estimated the dose equivalency of aripiprazole with respect to 4 mg/day of risperidone. A total of 41% of respondents considered aripiprazole at 15 mg/day to be the dose equivalent to 4 mg/day of risperidone, 33% chose 20 mg/day of aripiprazole, 15% chose 30 mg/day, 2% chose above 30 mg/day, and 9% of respondents chose 10 mg/day of aripiprazole as a dose equivalent for 4 mg/day of risperidone. It will be of interest to see how the dosing profile of aripiprazole evolves over time. There are some preliminary indications (see later section) that, at least for major depression, lower doses of aripiprazole are required.

Acute use of aripiprazole & the management of behavior emergencies

The development of a short-acting intramuscular formulation of aripiprazole has focused interest in the role of aripiprazole in treating acutely agitated patients. The intramuscular formulation of aripiprazole has been shown to be effective for acute agitation in patients with schizophrenia. Daniel and colleagues examined, over a 24-h period, the efficacy and tolerability of intramuscular aripiprazole (1, 5, 10 and 15 mg) and intramuscular haloperidol (7.5 mg) in a double-blind, placebo-controlled trial of acutely agitated patients with schizophrenia [12]. Both agents were superior to placebo in reducing agitation with the response (≥40% decrease in Positive and Negative Syndrome Scale [PANSS] Excitation Component) being seen at 30, 60, and 120 min for aripiprazole at the 10-mg dose. Haloperidol was effective at the 120-min time point. The other doses of aripiprazole were equal to placebo in effect (the 15-mg dose was more effective than placebo at 60 min). A total of six patients experienced dystonia – four on haloperidol, one on aripiprazole 10-mg dose and one on the 15-mg dose. Ari-piprazole was not sedating and did not cause pain at the injection site. There is also an analysis of pooled data from several registration trials, evaluating the effect of aripiprazole on hostility as measured by the PANSS Excitatory Component [29]. These data suggest that the calming effect of aripiprazole is seen across both schizophrenia and mood disorders. It must be noted, however, that the patients in these studies were not particularly agitated. There is also intramuscular aripiprazole and intramuscular lorazepam in acutely agitated patients with mania. Both drugs showed comparable efficacy in reducing agitation in this population.

There is initial information available from research on a new orally disintegrating form of aripiprazole. A study of the dissolvable oral formulation of aripiprazole in healthy subjects indicated that this formulation is well tolerated [11]. This may prove to be another option in the management of the acutely agitated patient.

Use of aripiprazole in first-episode schizophrenia

The pernicious course of schizophrenia has spurred efforts to identify and effectively treat this condition as early as possible. There are emergent data on the use of SGAs in first-episode psychosis. There is evidence available to support the use of risperidone, olanzapine or quetiapine in first-episode psychosis [30]. There is currently no information on ziprasidone in first-episode schizophrenia. In some contrast with the other SGAs, there is less information on the use of aripiprazole in first-episode schizophrenia. A 28-day, open-label trial provides preliminary information on aripiprazole in first-episode schizophrenia [31]. Among 20 patients with first-episode schizophrenia, patients received either 15 mg/day (n = 4), 20 mg/day (n = 5) or 30 mg/day (n = 1) of aripiprazole, given once daily. A total of 60% of patients demonstrated a clinically meaningful improvement. There were no clinically relevant Qtc or laboratory abnormalities and there was minimal change in weight. Only two patients experienced a 7% or greater increase from baseline weight. The results indicate that aripiprazole is an effective, safe and well tolerated antipsychotic in first-episode schizophrenia. Additional information on aripiprazole in first episode schizophrenia, including comparison with other SGAs, is required. Parikh and colleagues have recently reported on the impact of SGAs including aripiprazole on weight gain in adolescents with psychotic, mood, or behavioral disturbances who present early in the cause of their illness [32]. Waist circumference, body

mass index, and fat mass were each significantly increased in adolescents receiving either risperidone, olanzapine, quetiapine or ziprasidone. The effect of aripiprazole on these parameters was negligible.

Compared with first-episode schizophrenia, there is limited research on the treatment of prodromal symptoms. This is not surprising since this is provocative and challenging research, fraught with ethical dilemmas. There is no information on the use of aripiprazole in this unique patient sample.

Use of aripiprazole in the treatment of refractory schizophrenia

Information is emerging regarding aripiprazole's efficacy in refractory schizophrenia. An important and elegantly designed study of aripiprazole's efficacy in treatment-refractory schizophrenia has been reported by Kane and colleagues [33]. This study evaluated patients as treatment refractory based upon prospective treatment with SGAs. In addition to historical criteria of failed treatment response prior to entry into this study, patients were randomized to receive 6 weeks' treatment with either risperidone or olanzapine before being considered 'treatment refractory'. Thereafter, patients were randomized to 12 weeks' treatment with either aripiprazole or perphenazine. Both drugs attained similar responses on overall symptoms. Aripiprazole was reported to be significantly better than perphenazine on a measure of quality of life. Motor side effects were significantly lower in patients treated with aripiprazole.

There is also emergent information on the use of aripiprazole to augment the response of other SGAs in treatment-refractory patients. Duggal documented the response to augmentation with aripiprazole in a severely ill schizophrenia patient who had experienced only a partial response to olanzapine [34]. This may be a particularly advantageous choice in augmenting with two antipsychotics since it may minimize the additive effect of weight gain when combining SGAs. A similar strategy of adding quetiapine to clozapine resulted in improvements in glucose levels [35]. However, this approach requires rigorous evaluation. While the addition of aripiprazole (as an agent with a different pharmacologic mechanism of action) may be appealing, cost, adverse effects, and potential for drug interactions are important considerations [36].

Use of aripiprazole in the treatment of mood disorders

There has been a dramatic rise in the use of SGAs as monotherapy and combination treatment with mood stabilizers in the acute and maintenance treatment of mania. These drugs are emerging as effective and well-tolerated monotherapy or as adjunctive therapy in the treatment of acute mania bipolar disorder. Several agents have been examined in double-blind, placebo-controlled trials to determine their role in the treatment of acute mania and maintenance treatment of bipolar disorder [37,38]. Currently, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole have all received FDA approval for the treatment of acute bipolar illness; olanzapine and aripiprazole also have FDA approval for maintenance treatment of bipolar disorder. Also the combination of olanzapine/fluoxetine is approved for bipolar depression. An important study showing efficacy of quetiapine in bipolar depression has just been published. With regard to aripiprazole, there are now several studies evaluating aripiprazole's efficacy and tolerability in patients with mood disorders. These studies are predominantly short-term and focus on acute bipolar mania [39–42], although there is also information from a 6-month maintenance trial in bipolar patients. In a 3-week, placebo-controlled study of aripiprazole in acutely manic patients (n = 254), a 50% improvement was observed among 40% of patients receiving aripiprazole [39]. The effect of aripiprazole was seen an early as the day 4 of this 21-day trial. This pattern is similar to that reported in acute mania trials of other SGAs. Aripiprazole was well tolerated. In another short-term placebo-controlled trial, 41% of patients receiving 15 mg/day of aripiprazole responded, 45% of patients receiving aripiprazole at a dose of 30 mg/day responded. However, there was also a notably high response rate 38% in the placebo group [40].

A 12-week trial compared aripiprazole with haloperidol in 338 patients with acute mania [4]. Aripiprazole was initially given at 15 mg/day. After this initial period, investigators were permitted to use flexible dosing. The average study dose was 21 mg/day. Aripiprazole proved comparbale to haloperidol in response. There is also a recent subanalysis of pooled data from two 4-week studies examining the efficacy and tolerability of aripiprazole among the subset of patients (n = 171) who had a diagnosis of schizoaffective disorder [42]. Aripiprazole was efficacious and well tolerated in this patient population. These results essentially

mirror those of the main trials, indicating that the treatment response of aripiprazole in patients with mood disorders. There is also information available from a 26-week double-blind comparison of aripiprazole and placebo in the maintenance treatment of bipolar disorder [43]. Aripiprazole-treated patients lasted longer without relapsing and significantly fewer patients (18 vs. 27%) relapse compared with patients on placebo. There are also initial reports of the use of aripiprazole in bipolar depression and in major depression. Ketter and colleagues described an open-label trial of aripiprazole (mean dose 15.3 mg/day) in 30 patients with treatment-refractory bipolar depression [44]. There was a 27% response rate, with a 13% remission rate. Aripiprazole was generally well tolerated, although it is noted that 17% of patients developed hypomania. It may well be that this was an effect of the dose of aripiprazole used since another study also found that this patient population does not tolerate the 'usual' 15 mg/day) dose of aripiprazole. Simon and colleagues described a 8-week, open-labeled study of augmentation with aripiprazole in 15 patients with major depression who were poor responders to antidepressant therapy [45]. Aripiprazole augmentation was well tolerated, especially when patients were started at a dose of 2.5 mg/day. The study end dose was 7.5 mg./day. A benefit in symptoms was recorded. Further studies in these patients groups and more maintenance studies of aripiprazole are warranted. Brown and colleagues have recently reported preliminary findings of aripiprazole's effect in dual diagnosis patients [46].

Safety & tolerability of aripiprazole

Awad and colleagues provide a comprehension review of available studies of SGAs that examine their effect in terms of subjective tolerability and impact on quality of life patients [47]. There is only scant data on the impact on quality of life with aripiprazole. The benefit in quality of life in the refractory schizophrenia study with aripiprazole was described earlier [33].

Extrapyramidal side effects

Aripiprazole's propensity to cause extrapyramidal side effects, including tardive dyskinesia (TD), is important both with respect to its consideration as a SGA and also with respect to the clinical translation of its neuromodulatory effects as a partial agonist at D_2 receptors [48]. Tremor was observed in 7% of patients in the 26-week trial of aripiprazole [19]. There is an approximately 5% rate of akathisia observed in clinical trials [49]. Similar rates are recorded for aripiprazole in comparative trials with other SGAs. Akathisia was recorded in 11% of patients receiving aripiprazole (vs. 2% of patients on placebo) in the 3-week mania trial [39]. The effect of aripiprazole in bipolar depression or refractory depression has been mentioned above and it is unclear whether this represents akathisia, anxiety, mood activation, or some other effect. Overall; however, clinicians need to be aware that aripiprazole may induce akathisia, particularly early on in treatment. In clinical practice, this has been noted as a troublesome side effect in switching patients from another SGA to aripiprazole. Additionally, reports of EPS/agitation with aripiprazole have appeared in the literature [36,50,51]. The use of lower doses of aripiprazole and/or the short-term addition of a benzodiazapine appear to be effective in curtailing this adverse effect. A study evaluating akathisia is warranted. Current evidence suggests there is no signal of raised rates of TD in short-term or long-term studies of aripiprazole. This finding is in accordance with a recent analysis of available data on the incidence of TD with SGAs which reported the risk of TD to be approximately ten times less with SGAs than FGAs [52].

Weight gain & metabolic disturbances

Concern is now substantial regarding the risk of weight gain and metabolic disturbances with SGAs [53–56]. Using current evidence, aripiprazole appears to be less associated with weight gain than most other agents used in the treatment of patients with schizophrenia [56]. There is information on weight gain from several clinical trials. In the 4-week trial of aripiprazole versus haloperidol, both doses of aripiprazole were associated with less weight gain than in the haloperidol-treated patients [17]. In the trial of risperidone versus aripiprazole, the aripiprazole-treated group on average lost weight while risperidone-treated patients gained weight [18]. In the 1-year maintenance trial of aripiprazole and haloperidol, the weight gain was minimal between both agents [20]. The study of aripiprazole and olanzapine, showing superiority of aripiprazole over olanzapine for weight gain and metabolic parameters was described earlier [24,25]. This potential advantage for aripiprazole in lower weight gain and risk of endocrine/metabolic effects is important. The American Diabetes Association (ADA), in concert with the American Psychiatric Association and the American Association for Clinical Endocrinologists, summarized the evidence to date for antipsychotic – induced diabetes and related disturbances for each of the SGAs (**Box 1**). However,

Box 1. American Diabetes Association Consensus Conference recommendations on managing antipsychotic-induced obesity and diabetes.

- Consideration of metabolic risks when starting second-generation antipsychotics.
- Patient, family, and caregiver education.
- Regular monitoring according to current expectations and measurements.
- Appropriate referral to specialized service.

overall observations to date suggest that aripiprazole (and ziprasidone) both appear to have lower risk for these adverse effects than other SGAs. This impression will need to be confirmed or refuted by prospective long-term studies that are specifically designed to evaluate these adverse effects across each of the SGAs. Casey and colleagues, in a comparative analysis of available studies, suggest that the metabolic syndrome worsens with olanzapine but not with aripiprazole [57]. Data from clinical trials confirm that aripiprazole does not raise prolactin levels [49]. This is consistent with its effect as a partial agonist at D_2 receptors.

Other side effects

Either insomnia or sedation can occur early in treatment with aripiprazole. For most patients, changing the time of day for taking the medicine or a small dose reduction alleviates these difficulties. Aripiprazole does not appear to affect thyroid function, lead to cataract formation, or alter liver function tests. As with all antipsychotics, it has the potential to lower seizure threshold, but there is no evidence that this is any greater than any other SGA. Also, there is no evidence of clinically meaningful cardiac QTc prolongation during treatment with aripiprazole, another area of concern in the use of SGAs. Agranulocytosis and seizure risk is comparable to that of first generation antipsychotics. There is one recent report of neuroleptic malignant syndrome in a patient receiving aripiprazole [58].

Highlights

- Aripiprazole has a proposed preclinical mechanism of action, which complements its clinical profile.
- It is an efficacious and well-tolerated antipsychotic.
- In order to better appreciate its clinical potfolio, more information is required on:
  - Dosing
  - Use in special subgroups.
  - Tolerability over an extended period.
  - Comparative data with other second-generation antipsychotics.

Expert commentary

Aripiprazole offers patients and clinicians a useful treatment choice, taking into consideration its unique pharmacologic profile and its adverse effect profile. Dosing strategies for this drug, as well as its role in more refractory patients with schizophrenia remain to be clarified. On current evidence, the weight gain and metabolic profile of this drug is advantageous at a time when there is concern about the greater propensity of SGAs to induce these side effects. The propensity of aripiprazole to induce akathisia warrants more investigation.

In conclusion, aripiprazole is an effective antipsychotic with consistent effects on ameliorating overall positive, cognitive impairment, and negative symptoms of schizophrenia. The imminent availability of an acute intramuscular formulation will be a real asset in the acute care of patients. Its adverse effect profile is characterized by low risk for EPS and TD (but with an apparently greater propensity for akathisia than other SGAs), by minimal effect on prolactin levels, and by an apparently lower risk for weight gain and metabolic disturbances than most of the other SGAs. Additional long-term studies of aripiprazole and more head-to-head comparative studies with other SGAs will help determine the relative merits of this agent.

Outlook

The subsequent availability of multiple (oral tablet, dissolvable tablet, liquid solution, and acute intramuscular) formulations of aripiprazole will be important developments to the long-term use of aripiprazole. From present information, it is unclear what the implications of aripiprazole's neuromodulatory actions are from its off-label use, although this should be helpful to parkinsonism-related psychosis.

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