Twice a day dosing of aripiprazole

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ABSTRACT

Despite pharmacokinetic and pharmacodynamic evidence, unconventional dosing is seen in clinical practice. This article reviews data in the use of multiple daily dosing of aripiprazole, and agent with a long half-life that is indicated for once daily dosing.

KEYWORDS

aripiprazole, dosing interval, pharmacy and therapeutics

Unconventional doses and dosing intervals appear from time to time without rational justification. Whether it be aripiprazole two to three times a day, fluoxetine twice a day, divalproex sodium extended release twice a day, or bupropion XL twice a day, acceptance to this dosing is realizing an increase in pill burden (with the associated increase in cost), and an increase in risk for non-adherence. Psychiatric patients, known for their poor adherence rates, struggle to balance possible adverse events with the need to continue their medications as instructed. Only time will tell if these patients will maintain the repetitive routine of medication administration and make their appointments as scheduled. Historically, this has not always happened. So, why do patients need to take a medication more often than required, even at a subtherapeutic dose? The data, evidence, and clinical rationale presented here should help us understand the justification.

A sample of forty-two aripiprazole prescriptions was scrutinized for variations in dosing intervals and daily tablet quantities prescribed. Twenty-one patients had been taking multiple 2-mg tablets daily. Eighteen patients had been taking doses less than 5-mg daily for an average duration of 11 months, and thirteen aripiprazole prescriptions had a dosing interval greater than once daily. The interesting economic fallout here is the cost of all dosage strengths of aripiprazole from our supplier being equal and exceeding $8.50 per tablet.[1] The mission of the ensuing drug use evaluation was to provide options to the providers with a focus on cost containment and best practice in the adjunctive treatment of depression:

MISSION

- Search for data supporting the multiple dosing intervals of aripiprazole and the use of 2-mg tablets with dosing guidelines.
- Find evidence correlating dosing intervals with medication adherence and its effect on hospital re-admissions.
- Request the assistance of the Associate Chief of Staff for Behavioral Health and his staff of providers in developing a plan for best practice and cost avoidance.
- Recommend to the Pharmacy and Therapeutics (P & T) Committee best practice suggestions with a plan for cost containment.

A Medline search was done specifically for any research reporting once vs. multiple daily doses of aripiprazole. Sixty-nine abstracts were reviewed from that search and there was no mention of multiple daily dosing. The manufacturer's package insert presented two 6-week trials instrumental in obtaining an indication for adjunctive treatment of major depressive disorder. Efficacy of aripiprazole was established within a dose range of 2 to 15-mg/day, with gradual titration increases no less than one week apart, and 20-mg/day in the absence of potent CYP450 2D6 inhibitors.[2] Twice a day dosing was not documented.

In 2004, two 2-week double-blind, placebo-controlled trials showed short absorption and distribution half lives and a significantly longer elimination phase half-life averaging more than 68 hours with aripiprazole. The resulting steady state concentration on day 14 was found to be 4-6 times the initial Cmax on day one. This, and the determination of steady state concentrations being reached generally in fourteen days, supports the conventional dosing interval of once daily.[3]

Doses with multiple 2-mg tablets are the most perplexing to qualify given the following evidence. A 2009 study in *CNS Drugs* regarding the dose-response relationship of aripiprazole in schizophrenia and schizoaffective disorder

determined that, at doses of 2-mg, the striatal D_2 receptor occupancy exceeded the required amount needed for an antipsychotic response, although it was not considered to be clinically effective.[4] Initial doses may start with 2-mg daily in the dose titration and increased to effect over time according to an article by Bristol-Myers Squib Company and Otsuka Pharmaceutical in the Japanese Journal of Clinical Hematology, February 8, 2006, Dr John Zajecka, director of the Treatment Research Center at Chicago's Rush University Medical Center, added in the same communiqué that, "the availability of the Abilify® 2-mg tablet is important for physicians because it allows us to better meet the specific dosing needs of adults with Schizophrenia and Bipolar I Disorder".[5] There was no mention of adjunctive treatment in depression in the announcement.

Regarding lower multiple-daily doses, a physician once mentioned that care is taken to keep frail elderly patients controlled without the hassle of dealing with adverse effects. Some of the more common justifications for "spreading" the dose out in a 24-hour period include:

- To avoid side effects
- Patients were having breakthrough symptoms on a once daily regimen.
- Physician felt uncomfortable changing medications.
- When people are irregular in taking their medications, their doses are split throughout the day, so that if he/she refuses morning medications, the patient does not go the entire day without taking it.
- Abilify® does not come in a 40-mg tablet when this dose is required. The patient would be prescribed two 20-mg tablets whether he/she took them once or at split times.

Tolerability may provide vindication for twice a day dosing, but are providers overly sensitive to the complaints of the patients just starting this drug? Perhaps the answer is in the inter-patient variability of response and harmful effects, which is not discussed here. The two studies by Mallikaarjun et al. also looked at tolerability, and reported transient adverse effects early in the dosing period, but are rarely reported later, on days 11 and 14.[3] It is unlikely, however, that both 14-day trials had the ability to correlate tolerability with length of treatment.

A lower dose of aripiprazole may also be considered in patients who are CYP2D6 poor metabolizers or receiving a CYP2D6 inhibitor. CYP450 2D6 is one of three widely investigated candidate genes with known alleles involving the inactive isoform, which is classified as a poor metabolizer (PM) phenotype.[6] These variations in deoxyribosenucleic acid (DNA) coding could lead to increased concentrations of substrates. Accepting the cost and value of the information produced in genotyping with the AmpliChip®, the provider may choose to use lower doses of aripiprazole. Compounding this is the laundry list of enzyme inhibitors for CYP450 2D6, involved in changing the metabolism of aripiprazole if taken concomitantly. Antidepressants make up a solid portion of those inhibitors and can increase the plasma AUC up to 5-fold and/or decrease clearance as much as 80%.[7] Once recognized, the providers can also be prompted to consider a lower dose of aripiprazole. The following mnemonic may be used to remember potent and moderate inhibitors of CYP450 2D6:

The **P**arrot had **Q**uite a **F**lu **B**ug sin**c**e his **S**-**T**-**D**:

- Paroxetine
- Quinidine
- Fluoxetine
- Bupropion
- Cinacalcet
- Sertraline
- Terbinafine
- Duloxetine

Without the genotype test, initial lower doses may be considered an option if the patient has history of intolerance to medications that are substrates of CYP450 2D6. Possible toxic plasma concentrations caused by a PM phenotype could be an explanation to a patient's history of intolerability for such medications.

Rates of non-adherence in major depressive disorder vary from 28% after 1 month of treatment, to 52% after 3 months of treatment, and in schizophrenia as high as 72%.[8,9] Non-adherence makes it difficult for providers to increase an antidepressant or antipsychotic dose in order to achieve response long enough to maintain a baseline symptomatology. Adherence can improve, given an established residence, sufficient social support and positive life changes. Hospitalized patients, however, are more acutely ill. At discharge, any decrease in the ability to maintain economic and social viability may compromise stable housing and the attentive skill necessary to take medications regularly. Extending these challenges over time is sure to affect adherence and assure hospitalization again.[10] Strategies for improving adherence contain a mix of recommendations, and should never underestimate the value of a simplified dosing schedule, patient centered education on therapy and medications, and post-discharge follow-up. The quest for

once-daily dosing is still a good first step to helping patients manage their adherence to medications.

Data and evidence were presented to the Associate Chief of Staff of Behavioral Health, who subsequently approved best practice guideline recommendations with conditional acknowledgements, where therapy decisions by the psychiatrists are made:

- Knowing that clinical rationale prevails over reported evidence listed
- Verifying that safety and patient care will never be compromised
- With assurances that clinical decisions are patient-centered regarding doses and dosing intervals.=

The following recommendations were presented to the P & T Committee:

1. The removal of the 2-mg dose option in computer order entry- replaced with the 2-1/2-mg dose option (one-half of a 5-mg tablet).
2. Require a non-formulary pre-approval of any aripiprazole dosing interval more than once a day with documentation of clinical rationale in the patient's chart.
3. Recommend a dose of 5-mg daily to replace any 4-mg doses of aripiprazole using multiple 2-mg tablets.

The talents of a clinical pharmacist cover a wide spectrum of tasks, from solving pharmacotherapeutic problems, assuring medication safety, and maintaining the integrity of professional relationships. We are trained to make decisions rooted in evidence-based-medicine and published guidelines (augmented only by our clinical experience). There is, however, the option of biting one's lip knowing physician clinical experience has the advantages of provider empathy, observed acceptance, and the forethought of conservative therapy.

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