

## Nourianz® (istradefylline): A New Way to Switch Off Parkinson's

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**P**arkinson's disease (PD) is a neurodegenerative movement disorder that affects the substantia nigra region of the brain. Neurons in this section of the brain cannot produce the neurotransmitter dopamine which then leads to symptomatic PD.<sup>1</sup> This disease is most prevalent in patients over the age of sixty, affecting 1% of this population. In the United States, this disease has an annual financial burden of \$51.9 billion, with \$25.4 billion in direct medical costs and \$26.5 billion in non-medical costs.<sup>2</sup> Risk of developing PD increases with age (elderly), gender (males), and race (Caucasian). In fact, Diagnoses of PD are predicted to triple over the next 50 years as the average age increases.<sup>3</sup> Hereditary causes have not been directly linked to the development of PD, although some familial cases have been reported.<sup>3</sup> The LRRK2 or SNCA genes may be linked to autosomal dominant patterns while the PARK7, PINK1, or PRKN genes could be linked to recessive patterns.<sup>4</sup> Environmental factors such as exposure to pesticides, industrial chemicals, and exogenous toxins (trace metals, cyanide, lacquer thinner, organic solvents, carbon monoxide, and carbon disulfide) may also be associated with an increased risk of developing PD.<sup>5</sup> Smoking tobacco, caffeine and NSAIDs are thought to have an inverse association with PD risk, however additional epidemiologic and experimental studies are warranted.<sup>6</sup>

Symptoms of PD develop gradually and can vary for each individual. Usually, they will start on one side of the body with progression to bilateral presentation. These symptoms can be

characterized by a tetrad known as TRAP: Resting Tremor, Cogwheel Rigidity, Bradykinesia/Akinesia, and Postural reflex impairment.<sup>1</sup> A specific single-photon emission computerized tomography (SPECT) scan, called a dopamine transporter (DAT) test, can help support diagnosis if there is a suspicion of PD. Routine use of this test is not recommended, and there are no other lab or imaging tests that are recommended. Clinical diagnosis is the most common method of diagnosing PD and consists of observational symptoms of bradykinesia and at least one of the following, muscular rigidity, 4-6 Hz resting tremor, or postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Management of PD focuses on improving symptoms and the patient's quality of life. The period that patients have good motor system control is referred to as "on-time" and a period of decreased control is referred to as "off-time". Guidance for management of PD comes from the National Institute for Health and Care Excellence (NICE), which released guidelines in 2017.<sup>7</sup> Initial treatment should consist of levodopa for those in whom motor symptoms are impacting their quality of life and either levodopa, dopamine agonists or monoamine oxidase B (MAO-B) inhibitors for those whose symptoms do not affect quality of life. Dopamine agonists can be divided into ergoline and non-ergoline derivatives, with the ergoline-derived agonists not recommended until patients have developed dyskinesia or motor fluctuations despite levodopa therapy and whose symptoms are not controlled with a non-ergoline derivative. Ergoline derivatives include bromocriptine, cabergoline and pergolide.<sup>8</sup> Non-ergoline derivatives include pramipexole, ropinirole, rotigotine and apomorphine. For patients developing increased off-time adjuvant treatment to levodopa is recommended, taking the form of dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors such as entacapone or tolcapone.<sup>7</sup>

On August 27th, 2018 Nourianz® (Istradefylline), manufactured by Kyowa Kirin, Inc., was approved by the FDA to treat adult patients with Parkinson's Disease experiencing off-time episodes.<sup>9</sup> This novel medication is used with levodopa/carbidopa and targets the A<sub>2A</sub> receptor which can cause problems with movement. The purpose of this article is to review the safety and efficacy of istradefylline for the treatment of Parkinson's Disease.

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### CLINICAL PHARMACOLOGY

#### *Mechanism of Action*

The exact mechanism of istradefylline effects on motor system is unknown.<sup>9</sup> Preclinical in vitro and in vivo animals studies suggest istradefylline to be an adenosine A<sub>2A</sub> receptor agonist that acts through a non-dopaminergic mechanism to improve motor function.<sup>10</sup>

#### *Pharmacokinetics*

In a fasting state istradefylline reaches peak plasma concen-

tration at about four hours after administration.<sup>9</sup> Plasma protein binding is 98% and the volume of distribution is 450-670 (557L) liters. Istradefylline is primarily metabolized by CYP3A4, to a limited extent CYP1A1/1A2, CYP2C8, CYP2C9, CYP2C18 and CYP2D6. Roughly 39% of the drug is excreted in urine and 48% in feces. Steady-state is reached in about two weeks with a mean terminal half-life of approximately 83 hours. When administered with a high fat meal, plasma concentration increases by 64% and AUC by 25%, with a reduction in half-life of one hour. These differences are not expected to be clinically significant so it may be taken with or without food.

### CLINICAL TRIALS

The safety and efficacy of istradefylline was evaluated in four randomized, multicenter, double-blinded, 12-week, placebo-controlled studies (NCT00456586, NCT00199407, NCT00455507, NCT00955526).<sup>11-14</sup> Two of the trials are phase II and the remainder are phase III trials. Of these four trials, two of them were unpublished (NCT00455507 and NCT00199407). A summary of the results will be included in **Table 2**.

#### Phase II Trials

##### Study 1: NCT 00456586

LeWitt et al. conducted a phase II double-blinded, randomized, multicenter clinical trial that gathered information from 23 sites in the United States and Canada in order to determine the safety and efficacy of istradefylline compared to placebo in subjects with off-time symptoms.<sup>11</sup> To be included in the trial, the subjects were at least 30 years of age and able to give written informed consent. They had to have been diagnosed with idiopathic PD by the United Kingdom Parkinson's Disease Society criteria (UPDRS), which is used for motor evaluation and characterizes the extent and burden of disease. These criteria consist of a three-step process referring to the diagnosis of parkinsonian syndrome, classifying the exclusion criteria, and using the prospective supportive criteria for PD.

Further requirements included a modified Hoehn and Yahr Scale II-IV in the off-time state, a response with levodopa/carbidopa for 1 year (with a daily intake of  $\geq 4$  doses, or  $\geq 3$  doses/day if  $\geq 2$  were a sustained-release formulation), off-time lasting at least 2 hours per 24 hours via a self-reported home PD diary, and history of a stable regimen of levodopa/carbidopa at least 4 weeks prior to randomization. Patients were excluded from this study if they had been treated with liquid levodopa/carbidopa within 4 weeks of the randomization, treated with MAO inhibitors or if they had been treated with centrally acting dopamine antagonists within three months. Patients were also excluded if they had had neurosurgery, atypical parkinsonism or secondary parkinsonism, diagnosis of cancer or continuous cancer in the last five years or clinically significant illness of an organ system (ALT or AST  $>1.5x$  upper limit of normal). Further exclusions included a mini-mental status examination score of 25 or less, history of drug or alcohol abuse within two years, history of psychotic illness or seizures, clinically relevant depression disorder, history of neuroleptic malignant syndrome or were pregnant or lactating females.

The patients that met enrollment criteria were randomized in a 2:1 ratio to receive either istradefylline 40 mg per day (n=130) or placebo (n=66) for 12 weeks. The primary endpoint was the percentage of change from baseline in daily awake time spent in the

**Table 1 | Select Istradefylline Pharmacokinetics<sup>9</sup>**

<b>Absorption</b>	
<b>Tmax<sup>a</sup></b>	4 hours
<b>Cmax<sup>b</sup></b>	181.1 ng/mL
<b>Distribution</b>	
<b>Vd<sup>c</sup></b>	557 L
<b>Protein Binding</b>	98%
<b>Metabolism</b>	
<b>Hepatic</b>	CYP1A1 and CYP3A4
<b>Elimination</b>	
<b>Renal Excretion</b>	39%
<b>Fecal Excretion</b>	48%
<b>T1/2<sup>d</sup></b>	83 hours
<small><sup>a</sup>Time to maximum concentration; <sup>b</sup>Maximum concentration; <sup>c</sup>Volume of distribution; <sup>d</sup>Half-life</small>	

off-time state documented in a home PD diary. The key secondary endpoints included a reduction in the motor symptoms and improving activities of daily living from baseline reported by patient experience. The subjects would document their day by entering their predominant condition as asleep, "off", or "on" in 30-minute intervals. If dyskinesia occurred, the severity would be classified as "troublesome" or "non-troublesome". Participants were followed in outpatient clinics on two consecutive days during a seven-day period preceding the baseline visit and then at weeks two, four, eight and 12 to complete evaluations.

Overall, 172 of the 196 (88%) of patients completed the study. For the primary efficacy outcome, change from baseline in the percentage of daily awake time spent in the off-time state, istradefylline 40 mg daily resulted in a  $-10.8\% \pm 16.6\%$  (95% confidence interval [CI],  $-13.46$  to  $-7.52$ ) change vs placebo resulting in only a  $-4.0\% \pm 15.7\%$  (95% CI,  $-7.73$ – $0.31$ ),  $p=0.007$  between groups. This change from baseline in total daily awake off-time was  $-1.8 \pm 2.8$  hours for istradefylline vs.  $-0.6 \pm 2.7$  hours for placebo ( $p = 0.005$ ). For the secondary variable, on time without dyskinesia, istradefylline 40 mg daily showed a small increase (0.17 hours) over placebo which was not statistically significant. When comparing the on-time symptom without troublesome dyskinesia, istradefylline 40 mg daily resulted in an improvement over placebo by 0.96 hours over placebo ( $p = 0.026$ ). The study also found that the clinic responses to istradefylline occurred within two weeks of treatment initiation. Adverse effects were judged to be generally mild and well-tolerated with the most frequently reported events being dyskinesia, dizziness, insomnia, nausea, and accidents involving falls.

##### Study 2: NCT00455507

An unpublished phase IIb study funded by the Kyowa Kirin company compared the efficacy of istradefylline 20 mg/day and 40 mg/day for reducing the mean total hours of awake time spent in the off-time state in patients with advanced PD taking levodopa.<sup>12</sup> Patients (n=363) were randomized in a 1:1:1 ratio to double-blind treatment with daily doses of istradefylline 20 mg, 40 mg, or placebo for 12 weeks. The primary outcome was the reduction of

**Table 2 | Primary Endpoints from Intranasal Esketamine Phase III Trials<sup>11-14</sup>**

Trial	Trial Design	Primary Outcome	Intervention	Change (p-value)
NCT00456586 <sup>11</sup>	Phase II double-blinded, randomized, multicenter clinical trial	Changes from baseline in awake off-time to endpoint (%)	Placebo	-
			Istradefylline 40 mg	-6.78% (p=0.007)
†NCT00455507 <sup>12</sup>	Phase II, placebo-controlled, double-blind, parallel group, fixed dose study	Changes from baseline in daily off-time (hours)	Placebo	-
			Istradefylline 20 mg	-0.65 *p=0.028)
			Istradefylline 40 mg	-0.92 (p=0.002)
†NCT00199407 <sup>13</sup>	Phase III double-blind, placebo-controlled, randomized, parallel group, multicenter, fixed dose study	Changes from baseline in awake off-time to endpoint (%)	Placebo	-
			Istradefylline 20 mg	-4.57% (p=0.025)
NCT00955526 <sup>14</sup>	Phase III double-blind, placebo-controlled, parallel group, multicenter confirmatory study	Changes from baseline in daily off-time (hours)	Placebo	-
			Istradefylline 20 mg	-0.76 (p=0.006)
			Istradefylline 40 mg	-0.74 (p=0.008)

† Unpublished trial

the mean total hours of awake off-time time per day. The secondary outcomes of this study were to evaluate the efficacy of istradefylline 20 mg/day and 40 mg/day doses for reducing the mean percentage of awake time per day spent in the off-time state, evaluate mean change in the total hours and the percentage of awake time per day spent in the on-time state (without dyskinesia, with dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia), the change in UPDRS, and to evaluate change in Clinical Global Impression (CGI; a way to quantify and track patients progress and treatment response over time using a seven-point scale). The study also aimed to evaluate the safety of istradefylline 20 mg/day and 40mg/day doses. The primary outcome results were not available. However, the package insert for istradefylline mentioned that this study found an increase from baseline in on-time without troublesome dyskinesia of 0.57 hours (p=0.085) and of 0.65 hours (p=0.048), in the istradefylline 20 mg and 40 mg groups, respectively, when compared to placebo.<sup>9</sup>

### Phase III Trials

#### Study 3: NCT00955526

Mizuno and Kondo conducted a phase III multicenter, placebo-controlled, randomized, double-blind, parallel-group, and confirmatory study in Japan.<sup>13</sup> The purpose of the trial was to establish the efficacy of istradefylline 20 mg/day and 40mg/day doses in patients with advanced PD treated with levodopa. Patients included in this study were at least 20 years of age and must have had daily dosage of 300 mg of levodopa/decarboxylase inhibitor per day, a stable regimen of antiparkinsonian medications for at least four weeks prior to randomization, at least two hours of off-time per day, and stages two to four on the modified Hoehn & Yahr scale (off-time state). Patients were excluded with a history of neurosurgery for PD, transcranial magnetic stimula-

tion for PD within six months before randomization, dementia or a score of 23 or less on the Mini-Mental State Examination (MMSE). Women who were pregnant, lactating or planning to have children were excluded from the study. Additionally, anyone who had prior istradefylline exposure was also excluded.

Patients were randomized in a 1:1:1 ratio to double blind treatment with istradefylline 20 mg, 40 mg doses or placebo for 12 weeks. The subjects completed diaries for seven days before visits in weeks two, four, eight and 12. The primary outcome was change in mean total hours of awake time per day spent in the off-time state from baseline, recorded in diaries by the patients. The secondary outcomes included reducing the mean percentage of awake time per day spent in the off-time state, a mean change in the total hours and the percentage of awake time per day spent in the on-time state (without dyskinesia, with dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia), and a change in the UPDRS and CGI. Physicians also checked for adverse events during follow up visits.

The primary outcome, change in daily off-time, was significantly reduced in the istradefylline 20 mg/day (-0.99 hours, P = .003) and istradefylline 40 mg/day (-0.96 hours, P = .003) groups compared with the placebo group (-0.23 hours). There was no statistical difference between the istradefylline treatment groups (-0.99 hours vs -0.96 hours). The daily on-time without troublesome dyskinesia for placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day were 0.26, 1.09 (P = .003), and 1.08 (P = .004) hours, respectively vs placebo. The changes from baseline at end point for UPDRS Part II score (off-time) for placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day were -0.6, -1.4 (P = .03), and -1.7 (P = .009), respectively vs placebo. The changes from baseline at end point for UPDRS Part III score on-time for placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day were -2.8, -3.7 (P = .086), and 4.9 (P = .001), respectively, showing that istradefylline 40 mg/day significantly reduced UP-

**Table 4 | Adverse Effects of Istradefylline<sup>9</sup>**

Adverse Reactions (>10%)	
Dyskinesia	15-17%
Infrequent (1-10%)	
Agitation	1-2%
Confusion	1-2%
Constipation	5-6%
Delirium	1-2%
Diarrhea	1-2%
Dizziness	1-2%
Hallucinations	3-6%
Infections	2-6%
Insomnia	1-2%
Mania	1-6%
Nausea	4-6%
Paranoia	1-2%
Rash	1-2%

\$4707.50. There is a co-pay card program available that helps commercially insured permanent residents in the United States. Qualified individuals must pay the first \$20 of a 30 day supply, \$40 of a 60 day supply, and \$60 of a 90 day supply as long as their commercial insurance also covers istradefylline. Uninsured and cash-paying individuals are not eligible for the program.

**CLINICAL IMPLICATIONS**

The primary outcomes looked at subjective data using patient reported outcomes, which may potentially lead to bias that could overestimate or underestimate the effectiveness of the treatment. The authors were able to objectify the data using standardized ranking scales during initiation and in clinic follow-up for the secondary outcomes. The results suggest that patients get about 0.5-1 hour of additional control of their symptoms with istradefylline, which could very well be clinically significant to some patients. This may be hindered by the high cost of istradefylline. This is further confounded by the fact that the advanced average age of patients developing PD would likely qualify for Medicare, making a large portion of patients ineligible for the discount program. Additionally, a cost-effectiveness over long-term benefit analysis has yet to be determined, and no long-term safety data exists.

The trials evenly distributed the number of patients that received both doses as well as placebo, however a weakness of these trials was that they only compared istradefylline to placebo. Head-to-head comparisons of istradefylline against the myriad of other PD medications is warranted. NCT00456586 excluded patients taking other PD medications from the study while NCT00955526 included them as long as they were on a stable regimen for at least four weeks.<sup>11,12</sup> Most of the patients in this study had concomitant therapy with a dopamine agonist.<sup>12</sup> About half were either taking selegiline, entacapone, or amantadine. There were some patients taking anticholinergic agents and zonisamide. There was no consideration or analysis included for patients on multiple anti-parkinsonian medications. The trials used to approve this medication were all randomized and double-blinded, which is a strength

DRS Part III score. No differences were observed among the groups for other secondary efficacy variables. The most common adverse event was dyskinesia (placebo, 4.0%; istradefylline 20 mg/day, 13.0%; istradefylline 40 mg/day, 12.1%).

**NCT00199407**

Sussman directed an additional unpublished phase III double blind, placebo-controlled, randomized, parallel group, multicenter, fixed dose study (NCT00199407) in the United States to establish the efficacy of istradefylline 20 mg/day dose vs placebo for reducing the percentage of off-time in patients with advanced PD.<sup>14</sup> Patients (n = 230) were randomized in 1:1 ratio to receive either istradefylline 20 mg daily or placebo for 12 weeks. The primary outcome of this study was to reduce the percentage of off-time in patients with advanced disease that were already being treated with levodopa/carbidopa. Secondary outcomes included reducing the total hours of off-time, to evaluate the change in percentage of on-time, and to evaluate the safety of istradefylline 20 mg a day dose. Secondary outcomes also included evaluating changes in the UPDRS, Parkinson’s Disease Questionnaire (PDQ-39), Medical Outcomes Study 36-item Short form (SF-36), Patient Global Impression - Improvement scale (PGI-I), and CGI. The mean percentage of off-time was reduced by - 4.57% (p=0.025) from baseline in the istradefylline 20 mg group when compared to placebo. The results of this study were not published. However, the package insert indicates that the subjects that had received istradefylline 20 mg daily also had an increase in on-time without troublesome dyskinesia of 0.55 hours (p=0.135).<sup>9</sup>

**ADVERSE EFFECTS AND PRECAUTIONS**

Istradefylline in combination with levodopa may cause dyskinesia or exacerbate pre-existing dyskinesia. Clinical trials found that dyskinesia occurred in 15% of patients treated with istradefylline 20 mg, 17% of patients treated with istradefylline 40 mg, and 8% of patients treated with placebo who were also taking a stable dose of levodopa and aromatic L-amino acid decarboxylase inhibitor (e.g. carbidopa).<sup>9</sup> Dyskinesia was also the most common reason for drug discontinuation. Dizziness occurred in 3% of patients treated with istradefylline 20 mg, 6% of patients treated with istradefylline 40 mg, and 4% of patients treated with placebo. A list of common, infrequent and rare adverse effects can be found in **Table 3**.

**DOSING AND ADMINISTRATION**

Istradefylline is started at 20 mg once daily, in combination with levodopa/carbidopa for the treatment of PD and may be titrated based on response and tolerability, to a maximum dose of 40 mg once daily.<sup>9</sup> Patients that smoke more than 20 cigarettes a day should be started on 40 mg. This medication may be taken without regard to food. For patients with a Child-Pugh A score no adjustments are needed. In patients with Child-Pugh B score the maximum dose is 20 mg, and in severe hepatic dysfunction (Child-Pugh C) it is recommended to avoid the use of this medication. There is no need for renal adjustment, however use in patients with a creatinine clearance <15mL/min has not been studied.

**COST AND AVAILABILITY**

Istradefylline 20 mg and 40 mg for a 90 day supply will cost



of the approval of this medication. Two of those four trials that were used were published and only one of them was a phase III trial. While the unpublished trials may show efficacy, their lack of peer review could impact the ability to evaluate the true safety and efficacy of this drug. It should be noted that two of these studies were performed in Japan, so Asians accounted for 67% of the patient demographics and Caucasians accounted for 32%. This limits the generalizability of these studies especially since Hispanics have the highest incidence of developing PD, followed by Caucasians, then Asians.<sup>15</sup>

This is the first medication in the class, but the company Kyowa Kirin is working on A2a receptor agonist, KW-6356, that may provide more options for treating “off” symptoms.<sup>16</sup> There are multiple other classes of medications that are currently recommended for use in addition to carbidopa/levodopa. Until further trials are completed comparing istradefylline to the other classes, it is unlikely that it can be recommended over another medication at this time.

### CONCLUSION

Nourianz® (Istradefylline) is a novel A<sub>2a</sub> receptor agonist for the management of off-time symptoms in patients with Parkinson's Disease. The available evidence shows that istradefylline may be a safe and effective treatment option for those patients treated with levodopa/carbidopa and still experiencing symptoms. However, at this time it cannot be recommended over other adjunct agents with similar indications due to the lack of head-to-head comparisons.

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## PERSONALIZED MEDICINE CORNER

### Using Pharmacogenetic Testing to Inform Atomoxetine Therapy

Amanda Elchynski, PharmD

#### Background

To date, millions of children have been diagnosed with attention deficit/hyperactivity disorder (ADD/ADHD); it affects 9.4% of pediatrics (6.1 million) in the United States. Males (12.9%) are more commonly affected as compared to females (5.6%). Based on a survey conducted in 2016, six in 10 children will have another mental, emotional, or behavioral disorder in conjunction with their ADHD. Most commonly, children will have a behavioral or conduct problem, which affects five in 10 children with ADHD. The majority of children (three in four) receive treatment for ADHD, which includes medication management and/or behavioral treatment. It is estimated that of the 6.1 million children with ADHD, 62% are taking a medication.<sup>1,2</sup>

#### ADD/ADHD Pharmacotherapy

The American Academy of Pediatrics (AAP) guidelines for ADD/ADHD support the use of a stimulant medication (e.g., methylphenidate, amphetamines) as first-line treatment, unless the child is under six years old, in which case cognitive therapy is recommended. Non-stimulant medication like atomoxetine,

clonidine, and guanfacine are recommended if the child has failed stimulant therapy or if stimulants are contraindicated.<sup>3</sup>

### **Atomoxetine Mechanism of Action**

Atomoxetine is a norepinephrine reuptake inhibitor approved to treat ADD/ADHD in both pediatrics and adults. It works by inhibiting the norepinephrine transporter (SLC6A2) in the presynapses.<sup>4</sup> This blocks the reuptake of the norepinephrine into the presynaptic cleft, which leads to increased norepinephrine in the synaptic cleft to be utilized.<sup>5</sup> This increased norepinephrine can be utilized by the body to increase the patient's mood and ability to concentrate.<sup>6</sup>

### **Pharmacogenetic testing for guiding atomoxetine dosing: Is testing warranted?**

Atomoxetine is administered as an active drug which then undergoes metabolism by CYP2D6 to its metabolite, 4'-hydroxy atomoxetine, which is also active. However, the metabolite is rapidly metabolized into an inactive form by glucuronidation. CYP2D6 genotype has shown to have a variable effect on atomoxetine concentration. Patients who are CYP2D6 poor metabolizers (i.e., have no CYP2D6 enzyme activity) have increased concentrations of the parent compound and have been shown to have greater benefit with atomoxetine compared to non-poor metabolizers. These patients also have an increased risk of developing side effects, specifically increased heart rate, xerostomia, erectile dysfunction, hyperhidrosis, insomnia, and urinary retention as compared to non-poor metabolizers ( $p < 0.05$ ).<sup>7,8</sup>

In February 2019, The Clinical Pharmacogenetics Implementation Consortium (CPIC) released pediatrics guidelines on dose adjustments for atomoxetine based on the patient's CYP2D6 genotype. Regardless of the genotype, it is recommended to initiate therapy at 0.5 mg/kg/day if they are less than 70 kg, which is consistent with the FDA package insert.<sup>9</sup> The package insert recommends a target total daily dose of 1.2 mg/kg/day after three days.

In patients with normal to increased CYP2D6 activity, CPIC recommends increasing to this target dose after three days as well. However, in patients with reduced CYP2D6 activity (poor, intermediate, and normal metabolizers with an activity score of 1-1.25) CPIC recommends to obtain plasma concentration levels if no clinical response prior to increasing atomoxetine dose, suggesting that the lower dose of 0.5 mg/kg/day may be efficacious in this population group.<sup>10</sup>

Obtaining atomoxetine plasma concentrations may not be feasible or desirable depending on the clinical setting and patient-specific factors. While CYP2D6 genotype may not help guide initial atomoxetine dose, it can provide clinical information regarding which patients should be monitored for side effects, dose titrated more slowly (e.g., CYP2D6 poor metabolizers), and which patients should be monitored more closely for increased risk of therapeutic failure (e.g., CYP2D6 ultrarapid metabolizers).

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