

# A case report on the safety and efficacy of aripiprazole for depression in Brugada syndrome

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## Abstract

Brugada syndrome is a rare genetic cardiac abnormality that has been linked to aggravation of arrhythmias and sudden cardiac death through concomitant medication use, including psychotropic medications. This complicates the clinical team's approach to treatment of depression in patients with Brugada syndrome as many first-line psychotropic agents are recommended to be preferentially avoided. Aripiprazole, which has no formal recommendation for or against use in Brugada syndrome, is approved for augmentation treatment of major depressive disorder therapy. This case report details a male patient with a history of Brugada syndrome who was referred to an intensive outpatient program for worsening of chronic depression. Through a multidisciplinary, shared decision-making approach, aripiprazole was added to the existing regimen of bupropion and duloxetine for augmentation of depression therapy despite minimal evidence in Brugada syndrome. Patient adherence to aripiprazole therapy was reported for approximately 4 weeks with no significant electrocardiogram (ECG) changes compared with baseline. The patient noted subjective improvement in depressive symptoms with the addition of aripiprazole with an objective improvement in Quick Inventory of Depressive Symptomatology total score from moderate-to-mild symptoms. This case report describes 1 of the few cases documenting safe use of aripiprazole to augment depression therapy in a patient with a documented history of Brugada syndrome without potentiating a Brugada-pattern ECG, associated cardiac event, or worsening depression through almost 4 weeks of therapy. More studies regarding the effectiveness and safety of aripiprazole in the augmentation of depression therapy and safety in patients with Brugada syndrome are needed.

**Keywords:** Brugada syndrome, antipsychotics, depression, drug-disease interactions, aripiprazole

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## Background

Major depressive disorder (MDD) is a significant public health problem that affects 280 million people worldwide,<sup>1</sup>

causes an estimated 12 billion lost working days per year,<sup>2</sup> and has a suicide risk rate of approximately 15%.<sup>3</sup> Individuals with MDD may also have increased risk for anxiety disorders.<sup>4,5</sup> Many antidepressant options are available for treatment of depression. Evidence-based selection of antidepressant medications is based on standard guidelines as well as medication and patient-specific factors. Selective serotonin reuptake inhibitors (SSRIs) are usually recommended as a first-line treatment option but are not adequate treatment in 1 out of 3 cases.<sup>6</sup> Either changing or adding treatment is considered if SSRIs are not sufficient.<sup>7</sup> Other first-line treatment options include serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (ie, bupropion), serotonin modulators (ie, vortioxetine, vilazodone), and mirtazapine.<sup>8</sup>

This unique case report presents a patient with MDD, comorbid anxiety, and concurrent medical diagnosis of Brugada syndrome. Brugada syndrome is a rare genetic cardiac abnormality that predisposes patients to fatal arrhythmias,<sup>9,10</sup> thereby impacting psychopharmacologic treatment options.<sup>11</sup> Given the gravity of the risk, key pillars of management of disease and prevention of cardiac death include personalized risk stratification, multidisciplinary risk mitigation, and frequent follow-up.<sup>12</sup> Avoiding medications that may potentiate the electrocardiogram (ECG) abnormalities of patients with Brugada syndrome, specifically those that inhibit sodium (Na) channels, are a pivotal aspect of management given the proven association with adverse events.<sup>11</sup>

This case displays how an interdisciplinary medication review between a psychiatrist, a psychiatric advanced practice registered nurse, a cardiologist, and a psychiatric pharmacist contributed to a collaborative approach in treating a patient enrolled in an intensive outpatient program (IOP). Engagement of the patient in decision making led to initiation of aripiprazole in addition to preexisting duloxetine (SNRI) and bupropion with a good psychiatric outcome without cardiac complications.

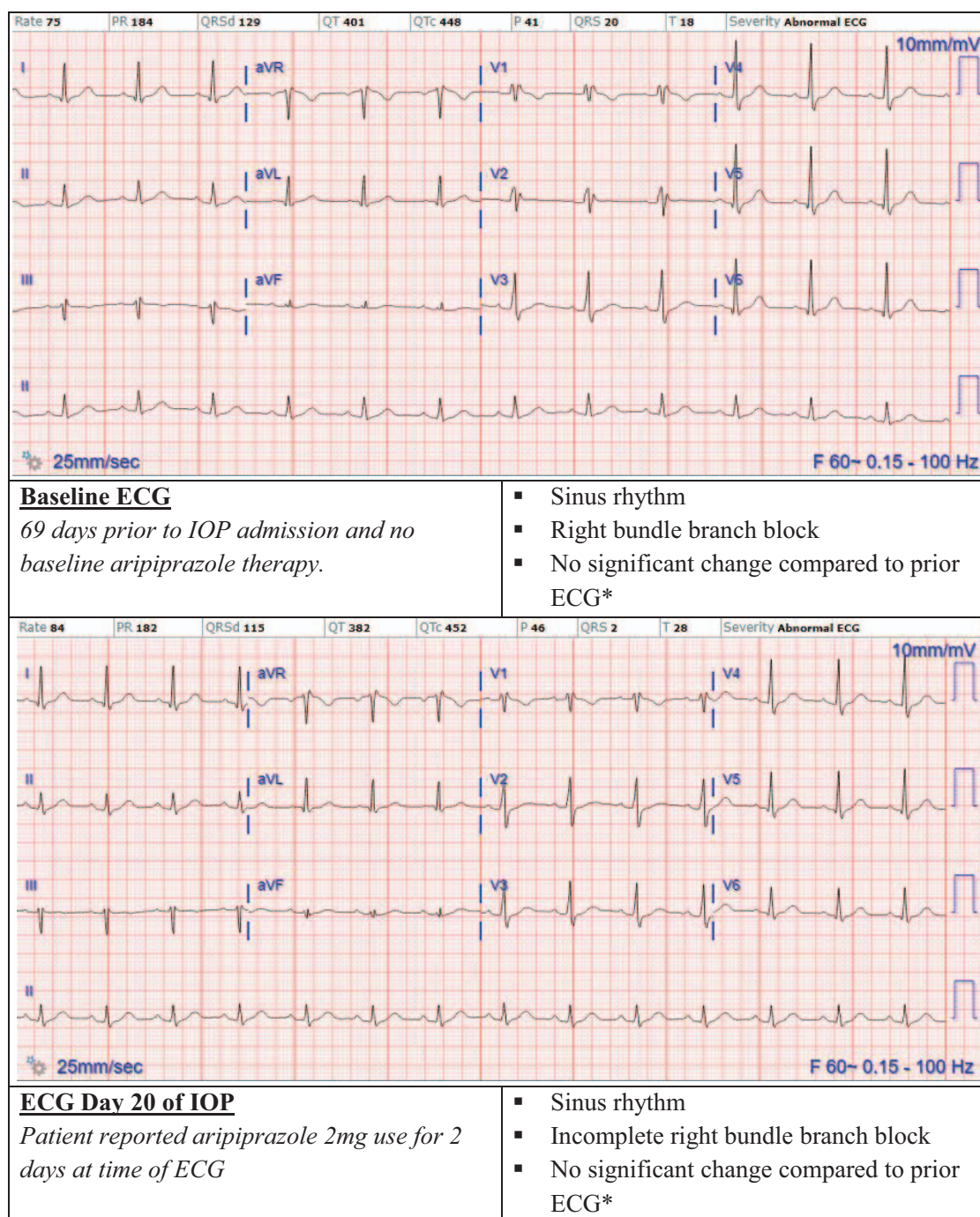
## Case Report

A 53-year-old male patient with a history of MDD without psychotic features, generalized anxiety disorder, social anxiety disorder, dysthymia, Brugada syndrome, irritable bowel syndrome, ulcerative pancolitis, eczema, plantar fasciitis, gastroesophageal reflux disease, and hypercholesterolemia was referred by his outpatient mental health clinician to an IOP for worsening of chronic depression. The patient expressed a rapid worsening in his mood for the past few weeks without an immediate precipitating cause on his current psychiatric medication regimen of duloxetine 100 mg daily, bupropion 24-hour extended release 300 mg daily, and lorazepam 0.25 to 0.5 mg as needed. Of note, the patient reported using lorazepam 0.25 to 0.5 mg every night for insomnia. His depressive symptoms included hopelessness, general lack of motivation, anhedonia, low interest, and passive suicidal ideation. He also reported the use of cannabis nightly through smoking and vaping for sleep and colitis symptoms without close provider follow-up but had no other form of cannabinoid use or substance use. The patient expressed concern about the reduced efficacy of his psychiatric regimen. Other medications at admission included esomeprazole, famotidine, probiotic tablets, multivitamin, and omega-3 fatty acids. His past psychiatric medication trials included escitalopram and other SSRIs (specific agents unknown), vilazodone, and mirtazapine. He also tried transcranial magnetic stimulation several years before this IOP admission, but its benefit was unclear. The patient presented as a clinical dilemma for the psychiatric team due to his refractory psychiatric symptoms in the setting of a history of Brugada syndrome, a cardiac abnormality that

has been linked to aggravation of arrhythmias and sudden cardiac death through concomitant medication use.<sup>11</sup> Furthermore, this patient was already using cannabis, a substance recommended to be avoided in Brugada syndrome, as well as bupropion, a medication that is preferentially avoided in Brugada syndrome.<sup>11</sup>

Given the patient's previous trials of medications, the interdisciplinary team considered initiating sertraline, vortioxetine, or aripiprazole for depression. Sertraline and vortioxetine are both first-line agents for depression and could have been considered as an alternative to duloxetine.<sup>8</sup> Adjunctive treatment with second generation antipsychotics (SGAs) has the most consistent evidence for efficacy in MDD, and aripiprazole, a SGA with partial dopamine and serotonin agonist properties, is listed as first-line for augmentation due to efficacy and tolerability.<sup>8,13</sup> A literature search was conducted to evaluate data on the use of sertraline, vortioxetine, or aripiprazole in patients with Brugada syndrome. Although sertraline is generally considered to be one of the safest SSRIs, it was shown to have cardiac sodium channel blockade properties and is recommended to be preferentially avoided in patients with Brugada syndrome. Vortioxetine and aripiprazole had no specific associated data indicating cardiac risk.<sup>8,11</sup> To ensure shared decision making, vortioxetine and aripiprazole were discussed thoroughly with the patient, and aripiprazole was ultimately selected to be initiated as an adjunctive agent for depression. This selection was discussed with the patient's cardiologist, who agreed that aripiprazole initiation was appropriate. The cardiologist recommended an ECG on day 1 of aripiprazole initiation and a repeat ECG approximately 1 week later. The interdisciplinary team also recommended limiting and ultimately discontinuing use of cannabis given the aforementioned guidance to avoid use in Brugada syndrome as well as the risk of amotivation and paranoia, which can mimic depression and psychosis.<sup>4,11</sup>

The patient began aripiprazole 2 mg nightly on day 18 of his IOP admission, and his Quick Inventory of Depressive Symptomatology (QIDS-SR) total score on this day was 14, which is interpreted as moderate depression. Response is defined as  $\geq 50\%$  reduction in baseline total QIDS-SR scores.<sup>14</sup> The patient's ECG completed on day 20 (Figure) of his IOP admission (after 2 days of aripiprazole therapy) showed no significant change compared with a baseline ECG. Aripiprazole was tolerated well overall with minor reports of fatigue versus insomnia, resulting in trialing aripiprazole administration at different times of day. The impact of aripiprazole on fatigue versus insomnia was confounded by cannabis use as the patient intermittently used cannabis throughout his IOP admission despite the recommendation that he stop its use. His ECG on day 34 (Figure) showed no significant changes compared with prior ECG (after 16 days of aripiprazole therapy). On day 36, aripiprazole was increased to 5 mg daily with the recommendation of

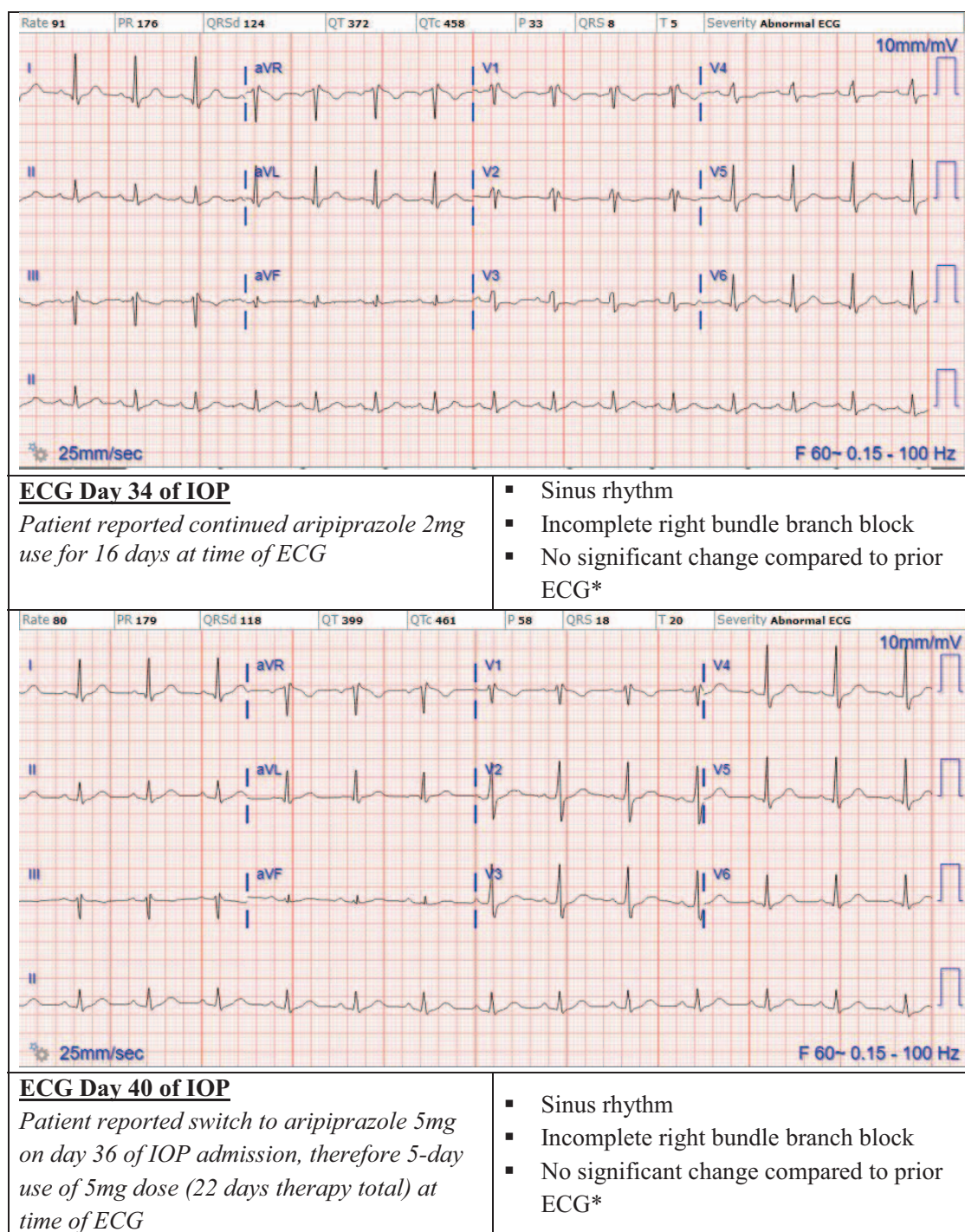


**FIGURE:** ECG findings through 43 days of monitoring

rechecking ECGs at 2 days and 5 days after dose increase per his cardiologist. His QIDS-SR total score decreased to 8, which is interpreted as mild depression and represents a 42% reduction in his baseline total QIDS-SR score. This was a clinically significant reduction in symptoms as reported by the patient. According to the QIDS-SR score, the patient demonstrated an objective reduction of symptoms from moderate to mild but did not meet the defined response of  $\geq 50\%$  reduction in baseline score. His ECG on day 40 (Figure) of IOP admission (after 22 days of aripiprazole therapy)

also showed no significant change compared to prior ECGs. The patient was discharged from the IOP on day 43 and reported “significant improvement in mood over the past 6 weeks,” which he attributed to a combination of pharmacotherapy and cognitive behavioral therapy. The patient also reported no use of cannabis since day 35 of IOP admission, and this abstinence may have further contributed to the improvement in symptoms. An ECG was completed on the day of discharge (day 43) (Figure), which showed no significant change compared with prior ECGs. His psychiatric





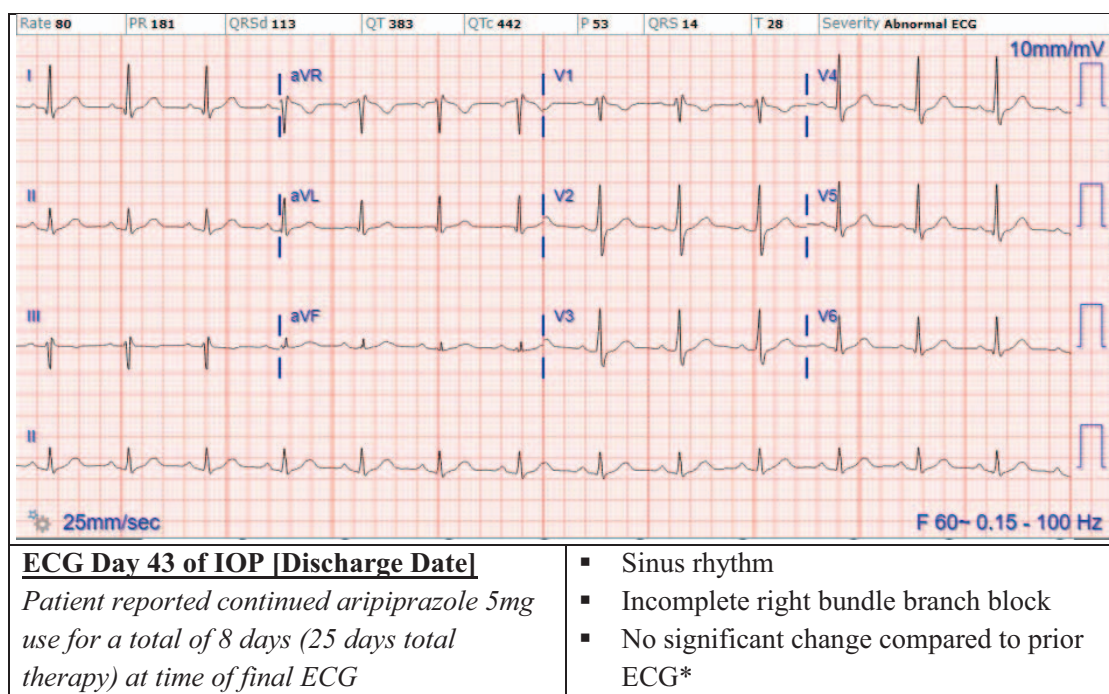
**FIGURE:** ECG findings through 43 days of monitoring (continued)

medication regimen on discharge was aripiprazole 5 mg daily, duloxetine 100 mg daily, bupropion 24-hour extended release 300 mg daily, and lorazepam 0.25 to 0.5 mg as needed.

## Discussion

Brugada syndrome is a rare genetic cardiac abnormality that predisposes patients to fatal arrhythmias.<sup>9,10</sup> Patients

may present with various phenotypes, genetic factors, and etiologies, including changes in calcium and potassium channels but most commonly with a loss of function mutation in the voltage-gated sodium channel gene SCN5A, occurring in 15% to 35% of patients.<sup>15,16</sup> The resulting syndrome is characterized by right bundle branch block and persistent ST-segment elevations in the precordial leads on ECG findings, which can result in ventricular fibrillation and sudden cardiac death.<sup>10,17</sup>



ECG = 12-lead Electrocardiogram, IOP = Intensive Outpatient Program

\*All ECGs were interpreted by the patient's cardiologist and therapy continuation was recommended

**FIGURE:** ECG findings through 43 days of monitoring (continued)

Specifically, many psychotropic medications have varying degrees of evidence displaying an association with adverse events in patients with Brugada syndrome and concomitant psychiatric disorders. This poses a significant problem for patients with depression as many first-line agents, including SSRIs and SNRIs,<sup>8</sup> are recommended to be preferentially avoided in patients with Brugada syndrome for risk of worsening cardiac events per an international expert panel.<sup>11</sup>

SSRIs used in depression, such as paroxetine,<sup>18-20</sup> sertraline,<sup>18</sup> and fluoxetine<sup>21-23</sup> have been reported to potentiate the typical Brugada syndrome ECG, but there is not yet substantial evidence beyond case reports and pharmacokinetic studies to suggest a direct correlation to fatal cardiac arrhythmias.<sup>11</sup> Whereas the data associating SSRIs with negative outcomes in Brugada syndrome are from a relatively weak compendium of evidence, the multidisciplinary psychiatric team may rightfully be hesitant to initiate or continue these agents given the potentially fatal risk<sup>12</sup> and infrequent epidemiology of Brugada syndrome.<sup>15</sup> An ex vivo study by Wang et al identified that, in rat pituitary GH3 cells and human embryonic kidney (HEK293) cells, both sertraline and paroxetine potently inhibited sodium channels in a state-dependent manner, a key potentiating factor in patients with Brugada syndrome.<sup>18</sup> This pharmacodynamic medication-disease interaction was shown to manifest in a 2010 case report by Sawhney et al in which the withdrawal of paroxetine 10 mg in a 48-year-old resulted in

the resolution of Brugada-pattern ECG.<sup>19</sup> Similar findings of the inhibition of cardiac sodium channels were observed in a molecular model of fluoxetine in HEK293 cells by Poulin et al in which they concluded a similar blocking to that of class 1 antiarrhythmics, and the need to consider this medication-disease interaction in patients with conduction disorders such as Brugada syndrome.<sup>23</sup>

These literature findings offered too high of a risk for the care team in this case, especially with additional data suggesting cardiac risk in Brugada syndrome with 2 of the patient's home agents, the medication bupropion<sup>11,24,25</sup> and the substance cannabis.<sup>11,26,27</sup> Thus, after a careful literature review, the use of vortioxetine as an alternate SSRI<sup>28,29</sup> and aripiprazole as a second-line or adjunct agent for the treatment of depression<sup>8</sup> were suggested to the patient as having little to no literature suggesting an association with Brugada-pattern ECG findings.<sup>11</sup>

Whereas vortioxetine had no data to support or negate its use, aripiprazole, a generally well-tolerated SGA, has often been studied for cardiotoxic effects and shown to have relatively safe outcomes.<sup>29</sup> A 2015 meta-analysis of 104 preclinical, clinical, and epidemiological/observational studies by Polcwiartek et al observed and summarized the cardiac safety of aripiprazole treatment patients at increased risk of Torsades des Pointes (TdP) and cardiac events. The 9 preclinical studies included suggested no significant QT-interval differences leading to TdP and did not assess sodium



current inhibition. Data from 61 patients in 37 case reports found no association between Brugada syndrome and aripiprazole treatment, and the remaining 51 clinical studies found no thorough QT interval studies upon which to draw conclusions. No epidemiological studies found an association between aripiprazole and Brugada syndrome, causing the investigators to conclude that aripiprazole likely had a low affinity for provoking the fast sodium cardiac channel.<sup>13</sup> A more recent and detailed analysis of the interaction between aripiprazole and the dominant voltage-gated sodium channel (VGSC) of the heart muscle (hNav1.5) was conducted by Fohr et al and found that aripiprazole inhibits VGSCs at low micromolar concentrations. As a result, these sodium channels recovered quickly in the setting of aripiprazole treatment, suggesting that that no cardiotoxic adverse effects should be expected.<sup>30</sup>

## Conclusion

The use of psychotropic agents in patients with concomitant Brugada syndrome remains a controversial topic with minimal evidence supporting their use and the risk of potentiating Brugada-pattern ECG findings or even fatal cardiac events. This case report describes 1 of the few cases known to investigators to document the safe use of aripiprazole to augment depression therapy in a patient with documented history of Brugada syndrome without potentiating a Brugada-pattern ECG, cardiac event, or worsening depression through almost 4 weeks of therapy. There were factors in this case that complicated the assessment of aripiprazole efficacy, including cannabis use/cessation and impact of other pharmacotherapy agents, but aripiprazole was deemed to be a safe option based on ECG results and a multidisciplinary risk-benefit discussion. More data regarding the effectiveness of aripiprazole in the augmentation of depression therapy and safety in Brugada syndrome is needed in the literature.

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