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Dasotraline: "New kid on the Bloc"

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Abstract

Attention Deficit Hyperactivity Disorder is a common neuro developmental disorder that can cause significant academic, interpersonal and adaptive impairments. Despite the development of several pharmacological options in last few years, search for an agent that is efficacious, has sustained clinical effects and without risk of abuse, continues. The need for such as agent is particularly critical considering the current opioid crisis. Sunovion Pharmaceuticals recently seeked FDA approval for one such agent Dasotraline which is a dopamine, serotonin and nor epinephrine reuptake inhibitor after preliminary trials established efficacy in adults and children with ADHD and Binge eating disorder in adult. We conducted a thorough review of the preclinical and clinical trials of this drug and used the information to summarize its safety, efficacy and tolerability in comparison to currently approved ADHD medications.

Keywords: Dasotraline; ADHD; Pharmacokinetics; Proof of concept trial; Misuse of stimulants

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a serious developmental disorder that affects individuals across their life span. The prevalence estimates of this disorder in adults is 2.5% based on recent studies [1,2]. Per a population study completed by the US National Association of Drug abuse, 16 million adults used prescription stimulants in the past year. Out of these, 5 million misused their prescription stimulants and 0.4 % met criteria for prescription stimulant use disorder [3]. A national multicohort study of high school seniors from Monitoring the Future study (2010-2011) showed that life time prevalence of medical and nonmedical use of stimulants is 9.5% [4,5]. These surveys have pointed towards a critical need in the field to develop efficacious pharmacological agents for the treatment of ADHD with lower abuse potential. Some of the currently available agents such as atomoxetine and alpha agonists that do reduce the risk of misuse have modest efficacy (0.6) and tolerability [6].

Mechanism of Action

Dasotraline [(1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene-1-amine] acts as a dual dopamine and norepinephrine reuptake inhibitor like psychostimulants such as amphetamine [7]. The distinction is the stronger norepinephrine reuptake inhibition of dasotraline in therapeutic dosages as compared to amphetamine. Structurally, dasotraline is a stereoisomer of desmthylsertraline, which is an active metabolite of sertraline, however, demonstrated weak inhibition of serotonin transporters at therapeutic dosages.

Clinical Effects

Several phase 1, 2, 3 trials have demonstrated efficacy and safety of dasotraline in the general population. Three phase 3 trials of 2-6 weeks duration in adults and children with ADHD showed moderate reduction in core symptoms of hyperactivity, inattention and impulsivity on ADHD RS IV scale. The reduction in scores was found to be statistically significant on 8 mg dose. A four week double blind placebo controlled trial showed an effect size of 0.41 on 8 mg and 0.25 on 4 mg daily dose [8]. Number needed to treat (NNT) of 8 was associated with more than 30% reduction in scores on 8 mg dose at week 4. In a separate 2 week randomized double blind lab classroom study in children 6-12 yrs. of age, an effect size of 0.85 was noted on 4 mg dose with significant reduction in ADHD symptoms over placebo [9]. In another 6 week once daily fixed dose dasotraline trial, only the 4 mg dose arm (as compared to the 2 mg dose arm) differed significantly from placebo in the hyperactivity and inattention subscale on ADHD rating scale IV [10]. A human positron emission

tomographic study of the drug completed by 9, 10 showed that dosages above 2 mg per day would be needed to achieve a blood level of 4.5 ng/ml which is required to achieve 50% DAT occupancy which is typically needed for effective control of ADHD symptoms [11-13].

Pharmacokinetics

The uniqueness of dasotraline lies in its pharmacokinetic properties of slow absorption (t max 10 hour post dose and long elimination half-life (ranging from 47-77 hours) which leads to stable plasma concentration over 24 hours with once daily dosing [14]. This can ameliorate one of the biggest clinical challenges for ADHD families of poor control of symptoms during the busiest times of the day (early morning and late evening hours). This pharmacokinetic profile of slow absorption and elimination lowers the drug's abuse potential. Spencer et al. assessed the potential for abuse and drug likability of dasotraline [15]. There were no differences between the 3 doses of dasotraline (8, 16, 36 mg) and placebo on the drug liking VAS at Emax [15] Methylphenidate at 40 mg and 80 mg dose had significantly higher VAS drug liking scores at Emax relative to placebo and all three doses of dasotraline. This allows dasotraline to have the potential to be an efficacious agent for treatment of ADHD without risk of misuse or abuse, hence, making it a very important treatment options for students on high school and college campuses where rates of diversion can be high. Misuse and diversion can lead to both increased medical risk including cardiovascular events and psychosis due to overdosing or poor medical monitoring of stimulant usage. This may also increase risk of creating access issues for patients with ADHD due to increased provider discomfort in prescribing medications that need constant monitoring for misuse [16].

Side Effects

The safety and tolerability of dasotraline was demonstrated in phase 2 clinical trial of 341 patients with ADHD [8]. Frequent side effects included dose dependent insomnia, appetite suppression and dry mouth. The most common adverse events leading to discontinuation were insomnia (2.6, 10.8 vs. 0% on 4 mg, 8 mg of dasotraline vs placebo), anxiety (2.6, 1.8, and 0) and panic attacks (0, 2.7, and 0). Only 10% of patients at 8 mg actually discontinued the medication due to intolerable side effects. Dasotraline was noted to have lower rates of GI side effects as compared to atomoxetine (10 % at 8 mg dose vs. 30% on atomoxetine). No notable effects on QTc prolongation or increased risk of suicide was noted.

Conclusion

Dasotraline is a dual dopamine and norepinephrine reuptake inhibitor under development for the treatment of ADHD in children and adults and Binge eating disorder in adults. Sustained treatment benefits beyond 24 hours with once daily dosing potentially will lead to early morning control of symptoms of this disorder which other long acting agents struggle to do. The effect size of 0.4 on 4 mg dose of dasotraline compares to that of non-stimulant medications for ADHD, pointing towards need for studying higher dosage of this medication for longer duration of time to achieve more impressive clinical benefits in adults. In children, however, impressive effect size of 0.85 persisting throughout the day was noted at the end of two weeks on 4 mg of dasotraline. Common side effects included insomnia, appetite suppression and dry mouth at rates comparable to current psychostimulants. The highlight of dasotraline is its slow absorption and elimination leading to lower drug likeability scores and risk of abuse, stable therapeutic response once daily dose as well as its unique ability to target early morning ADHD symptoms which can cause significant distress to families.

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