Combining 5-HT4R and DRD1 Gene Therapy Using AAV6.2FF: Improving Outcomes and Reducing Costs in Major Depressive Disorder

Executive Summary

Major Depressive Disorder (MDD), also known as clinical depression, is a chronic mental health condition characterized by persistent feelings of sadness, hopelessness, and a loss of interest or pleasure in daily activities. Unlike the typical fluctuations in mood everyone experiences, MDD is more severe and lasts for an extended period, often for weeks, months, or even longer, interfering with work, relationships, and overall quality of life. The prevalence of MDD in the United States has increased over the past 3 decades, with annual costs of treating MDD estimated to be approximately $210 billion annually,[1] including direct medical costs (such as healthcare services, medications, and therapy) as well as indirect costs (such as lost productivity, absenteeism, and reduced work performance). The exact cause of MDD is not fully understood, but it is thought to result from a combination of genetics, biological (imbalances in brain chemicals like serotonin and norepinephrine that are linked to depression), psychological and environmental factors (loss of loved one, financial stresses, etc.).

MDD can have a significant impact on a person's life, but is treatable. Current guidelines recommend antidepressant therapy for the initial treatment of MDD.[2] Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors (SSRIs) are the most common depression medication classes prescribed for initial treatment. However, antidepressants often require several weeks of continued treatment (due to receptor sensitivity, neuroplasticity, and/or involvement of multiple neurotransmitter systems) before a clinical response is achieved, which can lead to compliance issues. Adjunctive treatment, including the addition of another antidepressant from a different class, psychotherapy, or brain stimulation therapies, such as electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), and transcranial magnetic stimulation (TMS), will be used alone or in combination in severe cases which can be invasive and very costly.

This white paper explores an innovative approach in targeting both the serotonergic and dopaminergic systems in treating MDD. Pathways Neuro Pharma, Inc. (Pathways) gene therapy platform Adeno-Associated Viral Vector (AAV6.2FF) is designed to deliver the 5-HT4 receptor (5-HT4R) gene to the brain. By increasing serotonin receptor availability, Pathways' approach will enhance the efficacy of SSRIs such as Prozac (fluoxetine), Zoloft (sertraline), and other approved antidepressants at their initial doses potentially improving compliance and reducing the need for frequent re treatment(s). Additionally, incorporating DRD1 (dopamine receptor D1) will enhance dopaminergic function, addressing motivational deficits and further augmenting antidepressant effectiveness.

Pathways Gene Therapy Platform Adeno-Associated Viral Vector (AAV6.2FF)

Current SSRIs treatments often require dose escalation due to inadequate therapeutic responses, leading to increased side effects and reduced patient adherence. *AAV6.2FF enhances 5-HT4R expression, potentiating SSRI efficacy without increasing doses.* This targeted approach avoids dose-related side effects and overstimulation of other receptors, ensuring sustained therapeutic benefits while maintaining patient compliance.

Increasing Serotonin Receptor Availability

Increasing the availability of serotonin receptors (for example, by upregulating 5-HT1A receptors or improving receptor sensitivity) could potentially enhance the efficacy of SSRIs and lead to better outcomes with fewer adverse effects. SSRIs work by increasing serotonin concentrations, but receptor availability and sensitivity can influence how effectively serotonin binds to receptors and how strong the resulting effects are.

Improving receptor availability could lead to:

1. Faster Onset of Action: With more serotonin receptors available, the increased serotonin from SSRI use might have a more immediate effect.
2. Improved Compliance: If patients experience better or faster symptom relief, they may be more likely to stick with their treatment regimens.
3. Reduced Need for Dose Adjustments: If the serotonin receptor system is more responsive from the start, it might reduce the need for dose escalation or the addition of other medications over time.
4. Health Economic Impact: Escalating SSRI doses often necessitate higher medication costs and additional treatment for side effects. For example: Escalating Prozac from 20mg to 40mg increases the likelihood of treatment-emergent side effects by 30-50%, adding costs for additional medications and monitoring.

   AAV6.2FF Value Added: Preventing dose escalation reduces these incremental costs while maintaining efficacy.

Potential to Reduce SSRIs Side Effects

SSRIs increase serotonin levels by inhibiting its reuptake, but not all serotoninergic activity is necessarily beneficial. Some of the common side effects of SSRIs (such as sexual dysfunction, weight gain, emotional blunting, and sleep disturbances) may be partly due to excessive or unbalanced serotonin signaling in certain brain regions or receptor subtypes. By improving receptor availability, the following potential benefits could reduce these side effects:

1. Reduced Sexual Dysfunction: Upregulating 5-HT4R could potentially improve serotonergic signaling in areas where it may enhance mood without disrupting sexual function.
2. Reduced Emotional Blunting: Upregulating 5-HT4R could increase the serotonin system's ability to regulate emotional responses, making it more finely tuned and potentially preventing the emotional dulling that is sometimes associated with SSRIs.
3. Reduced Anxiety and Agitation: Early in treatment, some patients experience increased anxiety or agitation, which may stem from too much serotonin at certain receptors (e.g., 5-HT2A). Upregulating 5-HT4R could mitigate these side effects by promoting a more balanced serotonin response.
4. Less Weight Gain. Upregulating 5-HT4R could improve the balance of serotonin activity in these areas, potentially reducing weight gain associated with SSRIs.
5. Health Economic Impact**:** Side effects and poor adherence are major contributors to relapses and hospitalization in MDD, with an average cost of $15,000-$20,000 per stay.

   AAV6.2FF Value Added: Enhancing SSRI effectiveness and tolerability reduces non-adherence, lowering relapse rates and associated costs.

Prevention of Treatment-Resistant Depression (TRD)

Preventing treatment-resistant depression (TRD) in patients with major depressive disorder (MDD) is a complex challenge that requires a multifaceted approach, involving early identification, personalized treatment strategies, continuous monitoring, and proactive management. Patients with TRD often require high-cost interventions such as transcranial magnetic stimulation (TMS) or ketamine, averaging $6,000-$10,000 annually per patient.[3,4,5]

> **AAV6.2FF Value Added**: By maximizing the efficacy of first-line treatments, our therapy minimizes the progression to TRD, significantly reducing long-term healthcare costs.

Role of Dopamine and DRD1 (Dopamine Receptor D1)

Adding a dopaminergic component, such as enhancing dopamine receptor D1 (DRD1) activity, could further improve the efficacy of SSRIs, particularly for patients with motivational deficits, which are common in depression. The dopaminergic system plays a key role in motivation, reward processing, and pleasure, and its dysfunction is often implicated in the anhedonia (loss of pleasure) and low motivation that characterize MDD.

1. Improved Motivation: DRD1 activation enhances the functioning of dopamine in areas of the brain associated with motivation, goal-directed behavior, and reward processing (e.g., the prefrontal cortex, ventral striatum). Pathways' approach could address one of the most challenging symptoms of depression: lack of motivation.

2. Complementary Action: By combining serotonergic and dopaminergic modulation, Pathways might achieve a more comprehensive treatment that addresses both mood and motivational aspects of depression, potentially leading to better overall outcomes.

3. Augmented Antidepressant Effectiveness: Dopamine's role in regulating mood and energy levels, combined with serotonin's effect on emotional regulation, could enhance the efficacy of SSRIs, making them effective for a broader spectrum of depressive symptoms.

Regulatory Strategy

Positioning AAV6.2FF as an adjunctive therapy to existing approved SSRIs aligns with FDA pathways for enhancing existing treatments. This strategy shortens development timelines and leverages the established safety profiles of SSRIs.

Conclusion

Our AAV6.2FF gene therapy platform offers a paradigm shift in the treatment of MDD. By increasing serotonin receptor availability and enhancing dopamine receptor D1 activity, Pathways could theoretically enhance the efficacy of SSRIs, improve treatment response, and address both mood and motivational deficits in depression. This combined approach holds promise for more effective antidepressant therapies that require fewer adjustments, improving patient adherence and overall outcomes.

About Pathways Neuro Pharma, Inc.

Pathways Neuro Pharma, Inc. is developing the first pharmaceutical treatments that target the pathways in the brain that regulate and control the root causes of alcoholism, substance abuse, depression, and associated neurological conditions. Pathways is led by Bradley Thompson, Chief Technology Officer (CTO), with over 43 years of experience in autoimmune disease, oncology, and infectious disease, and Anthony Mack, President and Chief Executive Officer (CEO), with 35 years of experience in the pharmaceutical and biotech industries as a C-level executive overseeing the successful development and licensure of several innovative drugs in pain and addiction.

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