A Submission to the Therapeutic Goods Administration: Nomination for the Repurposing of Midodrine for the Indication of treating Postural Orthostatic Tachycardia Syndrome (POTS)

Authors: Marie-Claire Seeley & Celine Gallagher

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Orthostatic Hypotension and Postural Orthostatic Tachycardia Syndrome

Postural Orthostatic Tachycardia Syndrome (POTS) and Orthostatic Hypotension (OH) are both autonomic disorders characterised by dysregulation of blood pressure upon changes in posture, although they present distinctively. POTS typically involves an excessive increase in heart rate upon standing, often attributed to a hyperadrenergic state, while OH is characterised by a drop in blood pressure upon assuming an upright position. However, despite their differing clinical presentations and diagnostic criteria, both conditions share a common underlying mechanism driven by insufficient cardiac and cerebral venous return.[1-3] Treatment modalities targeting the augmentation of venous return and elevation of blood pressure are thus recommended for the management of both POTS and OH, acknowledging the interplay of autonomic dysfunction in their pathophysiology.[3-5]

POTS largely affects women of child bearing age and is associated with high disability and poor quality of life.[6] The escalating prevalence of autonomic dysregulation and the high incidence of POTS presentations in Post-Acute Sequelae of SARS-CoV-2 infection (PASC) were highlighted by evidence presented in the recently released findings of the Australian Parliamentary Inquiry into Long COVID and repeated COVID infections. Midodrine offers a therapeutic option for management of symptomatic autonomic dysfunction.[7, 8] Additionally, POTS is recognised as a common factor contributing to reduced quality of life in conditions such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and hypermobile Ehlers-Danlos syndrome (hEDS).[6, 8]

Despite the widespread use of 'off label' medications to manage symptoms associated with POTS, there are currently no medicines approved for use by the Therapeutic Goods Administration (TGA) and none are listed in Australia's Pharmaceutical Benefits Scheme (PBS). Approximately 25% of individuals with POTS are unable to attend work or education due to the disabling symptoms, further highlighting the burden of this condition and the potential impact of improved access to effective treatments like Midodrine.[9] However, the commercial viability of Midodrine poses a significant challenge to its potential sponsorship for TGA registration and PBS acceptance for Postural Orthostatic Tachycardia Syndrome (POTS). This challenge is primarily due to the poor clinical recognition of POTS and the select population that would benefit from its action. These factors may otherwise hinder the investment in Midodrine for formal regulatory approval and inclusion in government-funded healthcare schemes making it an ideal candidate for the TGA repurposing of medications program.

Midodrine Hydrochloride and Regulatory Acceptance

Midodrine has gained therapeutic acceptance for OH indications in major regulatory jurisdictions such as the EU, UK, USA, NZ, and Canada. In Australia it is indicated in **"*adults for the treatment of severe symptomatic orthostatic hypotension due to autonomic dysfunction when exacerbating factors have been addressed and other forms of treatment remain inadequate*".** Despite being recognised as a distinct disorder from OH since 1993, POTS has likely been excluded from therapeutic registrations due to the underrecognition of the disorder and the failure to appreciate its distinctiveness from OH. Indeed, a unique

International Classification of Disease code for POTS was only adopted in the USA in 2022 and has only just recently been accepted for inclusion in Australia's next iteration of ICD 10 which is due for implementation in early 2025. We are proposing that this exclusion be rectified through the repurposing of Midodrine as follows:

> ***"Indicated in adults and adolescents with severe symptomatic orthostatic hypotension, or postural orthostatic tachycardia syndrome due to autonomic dysfunction when exacerbating factors have been addressed and other forms of treatment remain inadequate."***

Evidence for use of Midodrine as a Treatment in POTS

Treatment of POTS is largely directed at symptomatic relief. The different classes of therapies used are as follows: 1. Reduction of heart rate; 2. Intravascular volume expansion; 3. Increasing peripheral vascular resistance (vasopressors). Midodrine is a short-acting vasopressor (fitting into category 3 above) which exerts its anti-hypotensive effect via stimulation of the alpha 1 adrenergic receptor, resulting in venous vasoconstriction and a subsequent elevation in blood pressure. Midodrine is an oral tablet, generally recommended to be taken at doses of 5-10 mg three to four times daily while upright due to its short-acting nature. This treatment modality focuses on symptom management, particularly for patients who are refractory to lifestyle changes such as salt and water loading. Improved venous return and increased cerebral perfusion and cardiac preload resulting from Midodrine administration is likely to enhance engagement in rehabilitation and reduce functional decline in those with severe orthostatic intolerance secondary to autonomic dysregulation.

The Canadian Cardiovascular Position Statement and the Heart Rhythm Society Expert Consensus Statement are considered the most comprehensive guidelines for POTS management.[1,2] The 2015 statement indicates that Midodrine significantly diminishes orthostatic tachycardia albeit to a lesser extent than intravenous saline.[2] While the more contemporary Canadian guidelines advocate a 'strong recommendation' with a moderate level of evidence for the first-line use of Midodrine in POTS patients manifesting low supine blood pressure.[1] These recommendations flow from several studies demonstrating the safety and efficacy of Midodrine in POTS. An initial study examined the effects of placebo, midodrine (5 to 10 mg), the alpha2-adrenoreceptor agonist clonidine (0.1 mg), and intravenous (I.V.) saline (1 L) in 13 patients who met the POTS diagnostic criteria.[10] Midodrine significantly decreased both supine and upright heart rate (HR) at 2 hours. Saline also decreased both supine and upright HR significantly 1 hour after infusion while Clonidine reduced supine HR but did not affect the HR increase with standing. Despite midodrine's known side effect of supine hypertension, it was observed to mildly decrease supine systolic BP in this study suggesting its action overall reduces hyperadrenergic responses.[10] The authors hypothesised that the use of alpha1-agonists like midodrine to replace lower-extremity postganglionic sympathetics may be a suitable therapeutic approach for patients with partial dysautonomia.[10] Subsequently, another study undertaken in an adult population compared the impact of midodrine and octreotide on objective parameters in individuals with POTS or orthostatic intolerance. The outcomes demonstrated that both agents were effective at reducing standing tachycardia although there was a failure to correlate this outcome to subjective improvement in symptoms.[11]

Midodrine has showed promising results in paediatric POTS studies. A study involving 14 adolescent POTS patients investigated the consequences of short-term intravenous administration of an alpha-1 adrenergic agonist, phenylephrine.[12] The authors found the drug improved orthostatic tolerance and haemodynamics with authors concluding that the findings lent support for use of oral therapy with alpha-1 agnosists such as Midodrine.[12] Another followed 53 children with POTS and compared the use of midodrine to metoprolol and conventional therapy. The study found a significant improvement of symptoms in the midodrine group within this paediatric cohort.[13] Another small study of midodrine has been undertaken in an adolescent and young adult population with POTS (mean age 16.5 years) in which the population was subdivided into a hyperadrenergic (n=8) or neuropathic (n=12) subtype.[14] The authors evaluated the impact of three times daily administered midodrine, up to 10 mgs for each dose if tolerated, over a two-week period. The results demonstrated reduced postural tachycardia in those with neuropathic POTS, with this effect not convincingly demonstrated in the hyperadrenergic subgroup (similar reduction in tachycardia with placebo and midodrine observed).[14]

Australian Clinical Practice

Midodrine is frequently utilised by clinicians treating POTS and related conditions in the Australian population. This is evidenced by a retrospective review of 300 POTS patients in a Melbourne cardiology clinic.[15] In total 62% of patients (83% female, 87% < 50 years age) experienced clear improvement over a median treatment duration of 24 months, with doses ranging from 5 to 30 mg daily.[15] Midodrine was ineffective in 23% of cases and ceased prematurely in 14% due to side effects. Importantly, 59% of patients received other medications for POTS during midodrine treatment with minimal interaction. This review suggests that midodrine frequently yields beneficial impacts on symptoms and lifestyle in patients with POTS, with a low frequency of side effects.[15] The Australian Dysautonomia and Arrhythmia Research Collaborative, University of Adelaide's therapeutic update recommends Midodrine's use to enhance alpha-adrenergic action in those with POTS. Additionally, Midodrine is routinely utilised by prominent clinicians such as Professor Dennis Lau (Cardiologist, Royal Adelaide Hospital), Assoc. Professor Chris O'Callaghan (Clinical Pharmacologist, Austin, Melbourne), and Professor Angus Hamer (Cardiologist, Box Hill Hospital, Melbourne), who have decades of experience in treating POTS in Australia. Unpublished data from the Australian POTS registry also reveals that 53% of POTS patients (n=165) were initiated on Midodrine treatment within a year of diagnosis, with 20% reporting it as the **MOST** beneficial treatment compared to lifestyle measures and other medications.

Summary

Midodrine emerges as an ideal candidate for repurposing efforts, meeting several criteria conducive to such initiatives. Firstly, it is a medication already approved for a similar disorder, having an already established safety and efficacy profile in similar patient cohorts. There is an established practice of using Midodrine 'off-label' for treatment of POTS in the Australian clinical context. Despite this clinical utility Midodrine's commercial viability remains low, making it unlikely to be sponsored for formal regulatory approval. Moreover, with the escalating prevalence of autonomic disorders and the absence of TGA-approved treatments for POTS, the repurposing of Midodrine holds significant promise in addressing unmet medical needs. Therefore, Midodrine warrants serious consideration for repurposing initiatives by the TGA.

Testimonial for Midodrine Hydrochloride Repurposing Nomination

My name is Bethany Wormald, and I want to share my journey of living with Long COVID-related Postural Orthostatic Tachycardia Syndrome and the transformative impact of Midodrine Hydrochloride.

As a full-time corporate marketing executive and regular amateur marathon runner, I was accustomed to the demands of a busy lifestyle. However, when I contracted a mild case of COVID-19, my life took an unexpected turn. Despite the initial infection being relatively mild, I found myself unable to fully recover. The severity of my orthostatic intolerance left me housebound for 11 months, unable to engage in everyday activities.

Doctors were at a loss for answers, and despite numerous attempts at rehabilitation, my condition showed little improvement. It wasn't until a cardiologist diagnosed me with POTS and started me on Ivabradine that I experienced some mild relief from my orthostatic intolerance.

However, I was still unable to return to work or exercise. It wasn't until I participated in the University of Adelaide POTS in Long COVID study that I was introduced to Midodrine. The difference Midodrine made in my life cannot be overstated. Before my POTS diagnosis, I couldn’t be upright for any length of time – even sitting up was a challenge. Despite trying various management strategies, my improvement was minimal, and I remained mostly housebound.

Then came Midodrine "off label". It was a revolution. Suddenly, I could stand upright again without debilitating symptoms. I returned to work three days a week, started gentle exercise, and felt like I was once again contributing to society. Three weeks after starting Midodrine I was back walking my regular 5km park run. Midodrine gave me back my independence and restored my sense of purpose.

Despite the financial cost, spending over $3,000 per year on Midodrine, I cannot imagine going without it. It has become an indispensable part of my daily routine, allowing me to live a more fulfilling and active life. While I am fortunate enough to be able to afford this medication, for many people the cost is untenable.

I urge the Therapeutic Goods Administration (TGA) to make Midodrine readily available by changing the current indication to include POTS. By doing so, countless individuals like me who are navigating the challenges of Long COVID-related POTS could benefit from this life-changing medication.

Bethany Wormald, Sydney, Australia

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