Exploring the Economic Benefits of Modafinil for Post-Stroke Fatigue in Australia: A Cost-Effectiveness Evaluation

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Background: In stroke survivors, post-stroke fatigue predicts dependency in daily living and failure to return to work. Modafinil shows promise as a pharmacotherapy to reduce post-stroke fatigue and related sequelae, e.g., poorer functional and clinical outcomes. *Aims:* This study explored the cost-effectiveness of modafinil in treating post-stroke fatigue in the Australian context, by determining its incremental cost-effectiveness ratio (ICER) and by simulating the potential cost-savings on a national scale, through a re-analysis of MIDAS trial data. *Methods:* A *post hoc* cost-effectiveness analysis was undertaken. Part A: patient-level cost and health effect data (Multidimensional Fatigue Inventory (MFI) scores) were derived from the MIDAS trial and analysis undertaken from a health-system perspective. Part B: a secondary analysis simulated the societal impact of modafinil therapy in terms of national productivity costs. *Results:* Part A: Mean cost of modafinil treatment was AUD$3.60/day/patient for a minimally clinically important change (10 points) in total MFI fatigue score, i.e., AUD$0.36/day/unit change in fatigue score per patient. For the base case scenario, the ICER of using modafinil (versus placebo) was AUD$131.73 ($90.17 – 248.15, for minimum and maximum costs, respectively). Part B: The potential productivity cost-savings to society were calculated as nearly AUD$467 million over 1 year, and up to $383,471,991,248 over 10 years, from the widespread use of modafinil treatment in the Australian population of working-age stroke-survivors, representing a significant societal benefit. *Conclusions:* Modafinil is a highly cost-effective treatment for post-stroke fatigue, offering significant productivity gains and potential cost-savings to society from the widespread use of modafinil treatment in the Australian population of working-age stroke-survivors.

Key Words: Modafinil—Stroke—Fatigue—Cost analysis—Cost-effectiveness

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Introduction

Post-stroke fatigue remains a substantial 'silent disability', affecting up to three-quarters of stroke survivors,[1,2] and rating among the worst symptoms experienced by nearly half of stroke survivors.[3] On the spectrum of stroke complications, fatigue receives considerably less attention than more visible physical disabilities,[4] despite fatigue adversely affecting clinical outcomes and quality of life, and being an independent predictor of institutionalisation, dependence in activities of daily living, poorer functional outcomes, and death.[1,5] In stroke survivors of working age, post-stroke fatigue is a major predictor of not returning to work.[6]

Unfortunately, the evidence base to inform strategies to reduce post-stroke fatigue has been limited by a lack of viable treatment options and/or robust studies.[7] Only a small number of non-pharmacological strategies (e.g., cognitive behavioural therapy) have demonstrated potential effectiveness, although none have been evaluated for their cost-effectiveness.[8,9] Relatively few pharmacological treatments have been trialled let alone shown to have any significant clinical benefits,[9] similarly for other types of fatigue (e.g., chronic fatigue syndrome). Recent attention, however, has focused on the potential role of modafinil – a eugeroic pharmacoetherapeutic agent (wakefulness enhancer) - which has demonstrated effectiveness in other conditions involving excessive daytime sleepiness, including obstructive sleep apnoea, restless leg syndrome, narcolepsy, depression and cancer.[10] In the context of stroke, the potential benefits of modafinil have been highlighted by the phase 2 randomised, double-blind, placebo-controlled, crossover MIDAS (Modafinil in Debilitating Fatigue After Stroke) trial.[11] In that trial, patients with post-stroke fatigue treated with modafinil for six weeks experienced a significant reduction in fatigue (i.e., mean reduction in Multidimensional Fatigue Inventory (MFI) score −17.38; 95% CI, −21.76 to −12.99; P<0.001), with improved quality of life (i.e., mean increase in Stroke-Specific Quality of Life score: 11.81; 95% CI, 2.31 to 21.31; P=0.0148), compared with placebo. Furthermore, modafinil demonstrated sustained benefits on 1-year follow-up, with minimal risk in terms of adverse drug reactions.[12]

Whilst larger phase 3 trials are needed to fully elucidate the effectiveness of modafinil in treating this silent disability,[13] it is inherently important to explore the potential economic implications of this therapy, given its probable scale of use in a global population of 25.7 million stroke survivors.[14] In Australia alone, where the financial cost of stroke is estimated to be $5 billion each year, the prevalence of stroke is expected to increase dramatically with a predicted one million people being affected by the year 2050, 30% of whom will be of working age[15,16] and thus most likely to be impacted by post-stroke fatigue. To date, there are no data regarding the cost-effectiveness of any intervention for post-stroke fatigue.

Aims

Noting the Phase 2 MIDAS trial findings,[12] the aim of this study was to explore the cost-effectiveness of modafinil in the treatment of post-stroke fatigue within the Australian context. The specific objectives were to: 1) determine the incremental cost-effectiveness ratio (ICER) for the use of modafinil (Part A); and 2) simulate the potential societal impact of modafinil therapy in terms of productivity costs, on a national scale (Part B).

Methods

The evaluation comprised two parts to examine the cost-effectiveness of modafinil from an Australian healthcare (Part A) and societal (Part B) perspective, applying the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[17]

PART A - Within-trial economic evaluation

A *post* hoc within-trial cost-effectiveness analysis (CEA) was undertaken based on the MIDAS randomised controlled trial (RCT) data.[12] A CEA compares health outcomes (e.g., life-years, changes in clinical parameters/health assessments, cases/events prevented) and costs of care (e.g., medication, supportive or adjunct care) between the intervention and an appropriate comparator or standard of care (e.g., usual care, placebo).[18] All costs and outcomes accrued during the RCT were analysed; where trial-based data were unavailable for input into the CEA, expert opinion was sought and unit costs assigned using government sources.

Population

Trial participants comprised 36 post-stroke patients aged ≥18 years, at least 3 months post stroke, with a score ≥ 60 on the MFI; 47.2% were of working age (<65 years). Participants received 6 weeks of treatment with modafinil (200mg oral tablets per day).[11]

Outcome measures

Fatigue (primary trial outcome) was measured using the Multidimensional Fatigue Inventory (MFI), a validated 20-item self-report instrument.[19] The MFI measures five fatigue domains: general fatigue; physical fatigue; reduced activity; reduced motivation and mental fatigue. Each domain item is scored between 1 and 5 to generate a summative domain score (to a total of 20) and overall MFI score (up to 100), with higher scores indicating greater fatigue. As the RCT did not adopt a multi-attribute utility instrument (i.e., EuroQol-5D) to assess patients' quality of life, no quality-adjusted life year (QALY) could be estimated.

Cost inputs

An Australian healthcare system perspective was taken to gauge costs; productivity costs were not considered within this perspective. Health care costs were based on actual cost-items incurred over the 6-week trial period, valued by the unit cost as at March 2019 (Table 1). Costs related to medication acquisition (i.e., modafinil supplied as a private, non-subsidised retail purchase) and outpatient care (i.e., excess specialist consultations to monitor patients on active treatment, additional blood tests for clinical chemistry/pathology) based on Medicare Benefits Schedule fees[20] were included. The non-subsidised unit cost of modafinil was sourced from the Pharmaceutical Benefits Schedule (PBS) and the quantity of modafinil consumed by each participant was extracted from patient-level RCT data. The costs of additional precautionary blood tests to identify any potential drug interactions post-commencement of modafinil were factored into the analysis. This included measuring coagulation parameters (i.e., International Normalised Ratio-INR), given that a large number of stroke patients would be taking anticoagulants as part of a long-term medication regimen (e.g., for secondary prevention of stroke); the cost of three additional INR tests (baseline plus two follow-up tests at 2 and 4 weeks) was added to overall treatment costs. The RCT did not document patient-level resource utilisation in relation to post-stroke management; instead, trial clinicians were consulted on the average number of excess specialist consultations and blood tests likely consumed by patients receiving modafinil (Table 1). It was considered that other post-stroke management (i.e., non-fatigue-related medical consultations) and medication costs (e.g., pharmacotherapy for hypertension, hypercholesterolemia, etc) would not be significantly different between the two randomised groups (i.e., these costs would be cancelled out in the calculation of the incremental cost). Further, it was noted that any other costs (i.e., physical, occupational, speech therapy) would vary mostly among those with significant physical disability, whereas modafinil use was reserved for those without significant disability who, in the absence of post-stroke fatigue, would otherwise be productive. Fatigue-related treatment costs

Table 1. *Part a inputs - health outcomes and cost of care.*

Input data for Base Case	Unit Cost	Treatment (Modafinil) A	Comparator (Nil therapy) B	Sensitivity Analysis Boundaries
Treatment effects per patient				
Mean change in MFI score (Modafinil vs Placebo)	-	−17.38	-	−21.76 to −12.99
	Treatment costs in AUD$ (Annualised) per patient			
Medication costs (200mg per day for 52 weeks)	$2.06 per 100mg tablet	$1,502.47	-	$1,358.81−$2,947.19 (lowest - highest cost)
Additional blood tests during treatment (full blood examination, Urea/Electrolytes/ Creatinine (U&E), liver function tests (LFT)) undertaken at baseline and at quarterly follow-up − 4 extra tests)	$29.50 per battery of tests (MBS items 65070 and 66512)	$118.00	-	$29.50−$206.50 (1−7 tests)
Additional coagulation tests during treatment (fortnightly instead of monthly − 12 extra tests)	$11.65 per test (MBS item 56120)	$139.80	-	$46.60 - $233.00 (4−20 tests)
Additional medical consultations during treatment (Quarterly specialist clinic appointments − 4 consultations)	$132.30 per consult (MBS item 110)	$529.20	-	$132.30 - $926.10 (1 - 7 appointments)
(Total cost)	-	$2,289.47	$0.00	$1,567.21−$4,312.79 (lowest − highest cost)
ICER = (Cost A−Cost B) divided by (Effect A − Effect B)	-	$131.73		$105.21−$214.86

MFI − Multidimensional fatigue inventory; CI − Confidence Interval; AUD$ - Australian dollars; MBS − Medicare Benefits Schedule.

for the comparator group (i.e., placebo) were considered negligible, reflecting the real-world situation of a patient receiving usual care (i.e., neither specific treatment nor extensive follow-up for post-stroke fatigue). All costs were expressed in Australian dollars (AUD) valued in 2019.

Analysis

Treatment costs were initially reported as the cost per unit change in MFI, and then the incremental cost-effectiveness ratio (ICER) was calculated as the summary measure. The ICER is the difference in the net *costs* of care divided by the difference in net *effects*, reported in monetary units as the cost per unit change in health outcome.[21] By definition, the lower the ICER, the better the cost-effectiveness of the intervention. In the absence of Australian thresholds for determining an ICER's acceptability,[21] the decision rule for this study was conservatively set at AUD $1,500 per year for an improvement in fatigue score, being higher than the ICERs reported from other modafinil studies (e.g., for use in psychostimulant dependence, ICER was AUD$79/stimulant-free day[22]) and higher than ICERs for other non-pharmacological interventions for fatigue syndromes (AUD$1,381/improvement in fatigue subscale[23]). Microsoft Excel™ was used for all algorithms and calculations.

PART B - Modelling the productivity cost of treating patients with post-stroke fatigue in Australia

Anticipating the likely magnitude of use of modafinil, a secondary analysis was undertaken to model the potential impact of treating the target population of stroke-survivors with post-stroke fatigue in Australia, i.e., on a national scale. A societal perspective was employed, first, to acknowledge that health interventions aimed at so-called "productive people" (e.g., employable persons) may derive substantial societal gains through improved productivity,[24] and second, to address the need to maximise social welfare as part of a good public health policy approach.[25] Productivity costs were defined as "*the costs associated with lost or impaired ability to work or to engage in leisure activities due to morbidity*",[26] incorporating production loss.

Population

Given the focus on productivity, the cost of treatment was simulated for the population of young persons with post-stroke fatigue across Australia. It was assumed that the population of working age stroke survivors (aged <65 years) with post-stroke fatigue was approximately 79,800 persons in the year 2019 (based on 30% of stroke cases in Australia being of working age,[12] and prevalence of post-stroke fatigue being 56%[1]).

Outcome measures

The treatment effect was defined in terms of improvements in fatigue as measured via the General Fatigue dimension on the MFI, with severe fatigue defined by a score ≥12.[6,27] Using this cut-off score to categorise the MFI data, severe fatigue was observed in 58.3% versus 77.8% of RCT patients in the modafinil and placebo groups, respectively.

Productivity was calculated in terms of employment, and the productivity cost attributed to post-stroke fatigue was calculated using the human capital approach,[24] i.e., employment income was used as a proxy for the production value of post-stroke survivors, acknowledging that patients with severe conditions (e.g., severe post-stroke fatigue) are less likely to return to work.[6] Data from a Danish two-year follow-up study of post-stroke patients were applied to the RCT data, noting that stroke care between the Danish and Australian health systems is generally regarded to be comparable in terms of access and quality.[28] First, return-to-work rates were identified: at the end of 1-year follow-up in the Danish study, 53.0% of patients with mild fatigue returned to work compared to only 28.1% of those with severe fatigue patients.[6] Second, the proportion of patients working full-time (72.7%) versus part-time (27.3%) was identified.[6] Then, mean Australian wage rates (38 hour working week) in 2019 were used as the base case (Australian Bureau of Statistics.[29] The total cost of lost productivity was estimated based on two scenarios: i) all patients with post-stroke fatigue receiving modafinil treatment or ii) all patients with post-stroke fatigue receiving no such treatment.

Cost inputs

Health care costs were informed by Part A and extrapolated to a period of 12 months to derive an annualised cost. Treatment costs comprised the purchase cost of the medication (modafinil 200 mg for 52 weeks), accounting for variability across different suppliers.[30–32] Associated costs included pathology tests (conservatively: 1 baseline test; 3 routine, quarterly follow-up tests; fortnightly INR testing) and fees for medical consultations in specialist clinics/consulting rooms[20], based on the Australian Government's PBS[30] or MBS[20]) All measurable cost variables were identified via consultation with the broader study team, guided by other cost analyses,[33] thereby ensuring that key costs were not overlooked.

Finally, in terms of overall societal impact, any potential savings from gains in productivity were calculated as the difference in annualised wages between modafinil-treated versus non-treated persons (taking into account part-time versus full-time employment), less the projected costs of health care. The base case focused on a 1-year time horizon, whilst a supplementary analysis explored the potential longer term impact on productivity costs over varied time horizons (2, 5, and 10 years). For the latter, weekly

earnings were adjusted by the Consumer Price Index[34] and treatment costs discounted at a rate of 3%, by convention.[35]

Sensitivity analysis

For both Part A and B, sensitivity testing was undertaken on the base-case (using actual mean costs and reported outcomes) to derive 'best-case' and 'worst-case' scenarios over a 1-year time horizon, and thereby identify those factors that most impacted on the cost-effectiveness of modafinil therapy and productivity gains. Sensitivity tests were performed by substituting the lower and upper bounds of the 95% confidence intervals for treatment outcomes and wages, and by using the lower and upper bounds (extracted from references/quotations) for unit costs. No additional or substitutive cost inputs were identified for inclusion in the analyses.

Results

Part A

Total modafinil treatment costs were calculated at a mean AUD$0.36 per day per patient (range $0.20 to $0.91) to achieve a 1-point decrease in total fatigue score (MFI). This translates to a mean cost of AUD$3.60/day/patient (range $2.00 to $9.10) to achieve a minimally clinically important change in total fatigue score (i.e., change in MFI of 10 points) and AUD$6.27/day/patient (range $4.29 to $11.82) to achieve a mean change in MFI score of 17.38 points (95%CI 21.76 to 12.99), as reported in the MIDAS trial.

For the base case scenario (i.e., achieving a clinically significant improvement in fatigue = 17.38 point decrease in MFI), the ICER for using modafinil (versus usual care, i.e., no treatment/placebo) was calculated as AUD$131.73, ranging from $214.86 to $105.21 when minimum and maximum values (across all inputs) were considered. For the worst case scenario (i.e., lower clinical effect with a mean MFI change of 12.99 and higher treatment costs), the ICER was $332.01. For the best case scenario (i.e., higher clinical effect with a mean MFI change of 21.76 and lower treatment costs), the ICER was $9.58. The sensitivity analysis revealed that the ICER was most sensitive to the impact of modafinil on MFI score. Among treatment costs, the ICER was most sensitive to the direct medication supply cost; using mean treatment effect, with minimum and maximum medication supply costs, the ICER ranged from $90.17 to $248.15, respectively. Throughout the sensitivity analyses, the ICER stayed well below the proposed $1,500 threshold, i.e., modafinil treatment was cost-effective in this context.

Part B

In comparing the potential impact of treating post-stroke fatigue with modafinil across the Australian population of stroke survivors, versus the costs of not treating, the calculated net saving to society from any gains in productivity (i.e., employment) was AUD $467,162,107.28 annually, i.e., just over AUD467 million (Table 2). These savings could be as high as AUD$ $639,728,668.74 (for the scenario where, irrespective of treatment, the background odds of returning to work were very low, with employment at a lower FTE among part-time employees, lower wages), representing a gain to society from increased productivity, but as low as AUD-$240,346,763.71 (in the unlikely scenario where, irrespective of treatment, the background odds of returning to work were very high, with employment at a higher FTE among part-time employees, higher wages). The sensitivity analysis revealed that savings from productivity gains were most sensitive to the impact of the overall odds of returning to work among those with severe post-stroke fatigue; when the odds were low (i.e., OR=0.17), irrespective of treatment, the gain in net productivity costs over 1 year could be as high as AUD$685,048,201.88, but as low as AUD -$204,653,351.06 where the background odds were very high (OR=1.64), i.e., in the latter scenario, modafinil treatment would result in a loss in net productivity costs.

Over the longer-term, the net gains in productivity costs were calculated as AUD$8,793,678,085.86 over 2 years (AUD$9 billion; range $2,171,230,307 - $10,031,981,911), AUD$82,964,503,421.15 over 5 years (AUD$83 billion; range $26,006,904,791 - $92,989,789,066.82), and $383,471,991,248.82 over 10 years (AUD$400 billion; range $125,444,958,039 - $428,239,612,915).

Discussion

Post-stroke fatigue receives comparatively less attention than other stroke complications, but is a major contributor to post-stroke recovery, particularly in terms of an individual's productive contribution to society and quality of life (i.e., employment). Our study shows that there are important economic implications too, noting that a relatively small investment in the cost of an effective treatment could derive huge cost-savings to the health-system and society – cost-savings which could ultimately be reinvested to further reduce the stroke burden in the Australian population.

At the first level, our study shows that, based on initial findings from the MIDAS trial, modafinil therapy is cost-effective, and costs as little as AUD$0.20/day per unit change in fatigue score per patient. Second, our study highlights the potential cost-savings in terms of productivity gains from the widespread use of modafinil in the Australian population of working-age stroke-survivors. By treating fatigue and increasing stroke-survivors' productivity, the society stands to save, on average, nearly AUD$467 million over 1 year, up to $383 billion over 10 years, by reducing the number of persons unemployed.

Table 2. *Part B Inputs - Simulating the potential impact of modafinil therapy in terms of productivity costs on a national scale.*

	Treatment (Modafinil) A	Comparator (Nil therapy) B	Cost-difference	Sensitivity Analysis Boundaries
Input Measures per patient, per year				
Total treatment cost in $AUD (medication plus associated treatment costs)	$2,289.47	$0.00	$2,289.47	$1,567.21−$4,312.79 (lowest − highest cost)
Productivity in terms of employment				
Odds (odds ratio) of person being treated for severe fatigue returning to work	0.53	0.53		0.17−1.64
Full-time equivalence (FTE) in returning to work	0.5 (half-time)	0.5 (half-time)		0.25−0.75 (quarter-time to three-quarter-time employment)
Average Australian wage (1.0FTE)	$1,634.00 (95%CI $1,614.01 -$1,653.99)	$1,634.00 (95%CI $1,614.01 -$1,653.99)		$817.00 (0.5 FTE to 1.5 FTE)
Productivity Costs across the population of stroke survivors (N=79.800)				
Total productivity cost (i.e., potential annual wages through employment)	$3,612,334,505.58 ($3,568,141,992.26−$3,656,527,018.90)	$3,896,796,906.86 ($3,849,124,342.50−$3,944,469,471.22)	$284,462,401.28 ($280,982,350.24−$287,942,452.32)	
Annual saving on productivity gained through treatment less incurred treatment costs**			$467,162,107.28 ($463,682,056.24−$470,642,158.32)	$639,728,668.74 (net gain)−$240,346,763.71 (net loss)

*total number of young stroke patients was 79,800 in 2019; ** health care costs include treatment cost, pathology tests, medical consultations; OR = odds ratio; FTE − full-time equivalent.

These savings are not insignificant noting that the financial cost of stroke in Australia, overall, is estimated to be $5 billion.

In interpreting the findings of this study, the methodological limitations must be acknowledged. First, this was a *post hoc* analysis, such that costing data were not specifically collected at the time of the MIDAS trial, and therefore some costs may have been missed and/or not accurately reported. Further, randomisation alone might not have controlled for all possible differences, including in the costs of other care (e.g., physical, occupational, speech therapies) between the treatment groups, also noting the smaller sample size. Second, the Part B hybrid analysis was simulated and based on the extrapolation of data from Part A, supplemented by relevant literature and/or published statistics. Third, the Part B analysis focused on adjusting the odds of returning to work for those with severe fatigue, and in doing so, may have potentially underestimated the return to work probability for those with mild to moderate fatigue. Additionally, the supplementary analysis (exploring longer term impact) modelled a particular cohort of stroke patients from a single year over varied time horizons (i.e., it did not simulate the addition of new patients in subsequent years), and further assumed that the treatment effect would be sustained over time. Finally, the findings are derived from a relatively small sample size, and are contextual and limited to the Australian population and funding arrangements of the Australian health-system, as informed by specific data from the MIDAS trial. Further evaluation is critically needed to fully elucidate the effects of modafinil in the treatment of post-stroke fatigue via a large phase 3 trial with concurrent costing and outcome data (including quality of life) to inform a robust cost-utility analysis.

Despite these limitations, this study shows much promise for the widespread use of modafinil as both a clinically viable and cost-effective treatment option, noting the conservative approach used in these analyses (i.e., assuming the highest possible treatment cost). The clinical and economic benefits of treatment might even be greater than informed by the MIDAS trial, if applied to even younger, working-age patients and excluding extensive precautionary blood testing in younger patients. Furthermore, the

societal benefit in improving the productivity of older persons (i.e., those over 65 years) through such treatment cannot be underestimated; grandparents who may be stroke survivors, for example, are an important resource and support (e.g., in terms of child minding) for working age parents. Likewise, the benefits of treating fatigue may play into other aspects of post-stroke care, for example, post-stroke fatigue may affect people's ability to cope with depression and stress.[36] Critically needed are higher-quality data to confirm the improvements to cognitive and functional post-stroke recovery afforded by modafinil, as reinforced by a recent meta-analysis.[37] Robust clinical trials would help to inform the future availability of modafinil as an approved and cost-subsidised treatment option on the Australian market.

Conclusion

Our study shows that modafinil is potentially a highly cost-effective treatment for post-stroke fatigue, costing as little as AUD$0.20/day per unit change in fatigue score per patient. This study also highlights the potential productivity cost-savings to society, of nearly AUD$467 million over 1 year, from the widespread use of modafinil treatment in the Australian population of working-age stroke-survivors.

Declaration of Competing Interest

The authors have no conflicts of interest to declare in relation to this study.

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