The Use of Amphetamines for Improving Cognitive Impairment in Patients with Multiple Sclerosis

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Recommended Citation
Kum, Hayley, "The Use of Amphetamines for Improving Cognitive Impairment in Patients with Multiple Sclerosis" (2016). School of Physician Assistant Studies. 586. https://commons.pacificu.edu/pa/586

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The Use of Amphetamines for Improving Cognitive Impairment in Patients with Multiple Sclerosis

Abstract
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Methods: An exhaustive search of available medical literature was conducted using MEDLINE-Ovid, MEDLINE-PubMed, Web of Science, and CINAHL. Keywords used included: amphetamines and multiple sclerosis. Relevant articles were assessed for quality using GRADE.

Results: Three studies have statistically significant improvements in some aspects of cognitive function in patients on amphetamines when compared to placebo. However, a high rate of adverse events were noted with L-isomer or D-isomer amphetamines alone.

Conclusion: Amphetamines positively impact cognitive function in MS patients. Mixed amphetamine salts extended release (MAS-XR) seemingly have the lowest rate of adverse effects with the greatest benefit per the Morrow & Rosehart study. Further research is needed to integrate this into a clinical setting.

Keywords: Amphetamines, multiple sclerosis
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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 13th 2016

Faculty Advisor: Elizabeth Crawford, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

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Acknowledgements

[Redacted for privacy]
# Table of Contents

Biography ......................................................................................................................... 2  
Abstract ............................................................................................................................. 3  
Acknowledgements ........................................................................................................... 4  
Table of Contents .............................................................................................................. 5  
List of Tables ..................................................................................................................... 6  
List of Abbreviations ......................................................................................................... 6  
List of Appendices .............................................................................................................. 6  
BACKGROUND .................................................................................................................. 7  
METHODS .......................................................................................................................... 8  
RESULTS ............................................................................................................................ 8  
DISCUSSION ...................................................................................................................... 13  
CONCLUSION ..................................................................................................................... 16  
References ............................................................................................................................ 19  

| Table I. Quality Assessment of Reviewed Studies | 19 |
| Table II. Summary of Findings | 20 |
**List of Tables**

Table I: Quality Assessment of Reviewed Articles
Table II: Summary of Findings

**List of Abbreviations**

ADHD...........................................Attention Deficit Hyperactivity Disorder
BDIFS.......................................................... Beck Depression Inventory Fast Screen
BRIEF-A...............................Behavioral Rating Inventory of Executive Function for Adults
BVMTR-DR.........................Brief Visual Memory Test-Revised, Delayed Recall
BVMTR-TL.........................Brief Visual Memory Test-Revised, Total Learning
CVLT2-DR...................California Verbal Learning Test, second edition, Delayed Recall
CVLT2-TL...................California Verbal Learning Test, second edition, Total Learning
FSS.................................................................Fatigue Severity Scale
LDX.......................................................Lisdexamfetamine Dimesylate
MAS-XR..................................Mixed Amphetamine Salts, Extended Release
MS.............................................................Multiple Sclerosis
PASAT..................................................Paced Auditory Serial Addition Test
SDMT..........................................................Symbol Digit Modalities Test
SGAC.............................................Subject Global Assessment
The Use of Amphetamines for Improving Cognitive Impairment in Patients with Multiple Sclerosis

BACKGROUND

Multiple sclerosis (MS) is a debilitating autoimmune disorder in which inflammation causes demyelination of the central nervous system. Cognitive impairment affects 40-65% of patients with MS and there is no current cure.1 While most treatments only target the physical deficits caused by the disease, cognitive impairment alone in MS patients negatively impacts work performance2 and may also influence relationships and decrease quality of life.3

Amphetamines are a stimulating class of drugs that increase the release of dopamine and inhibit the reuptake of dopamine in the brain. They are most commonly used to treat attention deficit hyperactivity disorder (ADHD), but they have been shown to increase working memory and attention in other mental illnesses as well.1 The concerns with this treatment are the potential for adverse events as well as abuse of medication. Amphetamines are among the top abused prescription medications in the US.4 There are also well-documented reports of adverse effects from amphetamines impacting development and causing central toxicity and psychological issues such as insomnia, negative affect, irritability, anxiety, and stimulant induced psychosis.4 However, in a recent review of more than 100 studies, amphetamines and amphetamine containing medications are well-tolerated by most patients even when taken for several years.4

The literature reveals that several types of amphetamines have been trialed to treat cognitive deficits in MS. The first inquiries into this topic stemmed from the use of amphetamines found to improve memory and attention not only in ADHD but also in
Further research reveals that amphetamines improve reaction times, visual/spatial attention tasks, and the accuracy of working memory in patients with traumatic brain injury. The nature of impairment to the brain in MS is similar to an injury, but by an autoimmune process rather than direct trauma. Due to the lack of treatment for MS patients with cognitive deficits and this connection in literature linking amphetamines and cognitive improvement, this area of research has begun to develop. This review aims to assess the evidence for using amphetamines to treat or improve cognitive impairment in MS patients.

METHODS

A comprehensive and exhaustive literature search was completed in three databases: MEDLINE, Web of Science, and CINAHL. On each database, “amphetamines” and “multiple sclerosis” were the only key search terms used. Search filters included only human studies that were published or translated in the English language. The method of measuring cognitive function was objective using a validated scoring system in each study. Studies were excluded if they were conducted greater than 10 years ago, if there were fewer than 30 patients that completed the trial, and if they were not current randomized control trials. Each study in this systematic review was critically appraised and graded for quality and validity. The grade and limitations are summarized in Table 1.

RESULTS

The MEDLINE search displayed 16 studies on Ovid and 15 studies on Pubmed. Web of Science found 29 studies and CINAHL revealed 1 study. Of the 61 total studies found, duplicates were excluded and three met the inclusion and exclusion criteria set prior to the search. The three
studies were conducted on patients with cognitive impairment due to multiple sclerosis, evaluating the use of amphetamines in comparison to placebo, and measuring cognitive function. Each study analyzed a different type of amphetamine for intervention. All studies were randomized control trials. The inclusion and exclusion criteria limited the population to patients with cognitive impairment due to MS and took measures to minimize the risk of confounding factors.

They each used a validated objective measure for cognitive function, but they were slightly different for each study. The Symbol Digit Modalities Test (SDMT) measures visual processing speed by quick oral association of symbols with a previously matched digit. The Paced Auditory Serial Addition Test (PASAT) measures auditory processing speed by tasking participants with quickly adding two verbally given digits. The California Verbal Learning Test, second edition, Total Learning (CVLT2-TL) and Delayed Recall (CVLT2-DR) measures auditory and verbal learning with an interference and a delay after words are read to the participants. The Brief Visual Memory Test-Revised, Total Learning (BVMTR-TL) and Delayed Recall (BVMTR-DR) measures visual and spatial memory by showing participants geometric shapes and having them draw the shapes after an interference and a delay. At least two of these measurements as well as a few others including subjective self-rating tests are taken at baseline and at the end of the trial in each study. A summary of these tests and the findings of each study are summarized in table II.

Morrow et al (2009)

In this study, L-amphetamine was analyzed for improvement in cognitive function in clinically defined MS patients. The authors hypothesized that the L-isomer of amphetamine, while less potent in increasing dopamine, increases the amount of norepinephrine in the
hippocampus and cortex. This mechanism could theoretically increase processing speed and memory with fewer side effects than the D-isomer, which is commonly used as psychostimulant in appetite suppression and attention deficit disorder.\textsuperscript{6}

They tested this hypothesis with a group of 151 clinically defined MS patients that were cognitively impaired based on conventional norms of in the SDMT, CVLT2-TR, or PASAT. The intervention and placebo groups were randomized by a computer program in a 2:1 allocation and complete concealment from all participants and clinic staff with the exception of the pharmacist supplying the medication. The final sample included 136 patients, 99 received treatment and 37 placebo. No significant differences in demographics or prognosis between the intervention group and control group were found. Participants in the intervention group were started on 5mg and titrated up to 30 mg over 14 days. They continued on a maximum of 30 mg until day 29.\textsuperscript{6}

The primary outcomes are the Subject Global Assessment (SGAC), a subjective self-rating of cognitive function, and the SDMT, an objective visual processing speed and working memory score. Secondary outcomes were the CVLT2-TL, CVLT2-DR, BVMTR-TL, BVMTR-DR, and the PASAT. The scores of these tests were measured at baseline and day 29, then statistically analyzed. Adverse events were reported in 71.3\% in the intervention group and 58.1\% in the placebo group. Five participants withdrew due to the events.\textsuperscript{6}

Delayed recall in both auditory/verbal learning (CVLT-II) and visual/special learning (BVMT-R) improved by 48.5\% in memory impaired patients with MS on L-amphetamine compared to 1.0\% on placebo. In the original study, there were no significant findings for the primary outcomes, but there were significant results for secondary outcomes. These outcomes were reanalyzed by Sumowski et al.\textsuperscript{6,7}

\textit{Morrow et al (2013)}
The aim of this study\textsuperscript{8} was to determine if lisdexamfetamine dimesylate (LDX), a prodrug that converts to a D-amphetamine, will enhance the cognitive function of MS patients with a documented deficit in processing speed or working memory over the duration of 2 months. They were also assessing for tolerance to the medication and self-reported improvement in quality of life.\textsuperscript{8}

They study included adult males and females with definite MS per 2005 McDonald criteria with an Expanded Disability Status Scale core of $\leq 6.5$ and a minimum of 1.5 standard deviations below the mean on either of the primary outcome measures based of previously reported normative data. Of the 63 enrolled and randomized, 48 completed the 8-week study with 29 in the LDX group and 19 in the placebo group. Participants started on 30 mg and titrated to 70 mg daily. The outcomes were measured at baseline, day 29, and day 57. There were no significant differences found in demographics and prognosis between groups.\textsuperscript{8}

The primary outcomes were the SDMT and PASAT. The secondary outcomes are the CVLT2-TL, BVMTR-TL, and Behavioral Rating Inventory of Executive Function for adults (BRIEF-A) as a self-perception rating of capacity for activities of daily living. Other secondary outcomes assess fatigue with the Fatigue Severity Scale (FSS) and depression or mood with the Beck Depression Inventory Fast Screen (BDIFS). There were significant differences found in the baseline scores between the two groups. The LDX group had a greater cognitive impairment in SDMT, BVMTR-TL, and BRIEF-A scores. The adverse events were reported to be 79.3\% in the intervention group, but also high in the placebo group at 68.4\%. The side effects most frequently reported in the intervention group were dry mouth, headache, palpitations, nausea, decreased appetite, and anxiety. At least one patient in the LDX group withdrew from the study due to an
intolerable adverse event. Although none of these events were serious, there was found to be an increased heart rate and blood pressure in the LDX group.\textsuperscript{8}

All quantitative outcomes produced a positive trend; however, only SDMT and CVLT2-TL showed statistically significant improvement in cognitive function defined by a p-value of less than or equal to 0.05. In the SDMT, the mean score increased by 4.6 points in the LDX group compared with 1.3 in the placebo group. In CVLT2-TL, participants in the LDX group increased their scores by an average of 4.7 points compared to 0.9 points on the placebo. A nonsignificant trend is shown in the PASAT and BVMTR-TL scores. This study also made note of all adverse events between the two groups, which was a high proportion.

**Morrow & Rosehart**

This study\textsuperscript{9} set out to determine if mixed amphetamine salts in extended release form could have a positive effect on cognitive function in MS patients. The extended release formulation may have less risk for abuse and side effects than other forms of amphetamines. The theory behind this thought is that there is a more controlled and steady rate of release of dopamine levels in the brain.\textsuperscript{9}

They conducted a randomized controlled study looking at the cognitive function before and after a single dose of mixed amphetamine salts, extended release (MAS-XR). Patients were split 1:1:1 into three groups: MAS-XR 5mg, MAS-XR 10mg, and placebo. There were 62 patients selected to participate based on inclusion and exclusion criteria that were randomized by computer program. This included only patients that suffered from cognitive deficits that were caused by MS minimizing the possibility for confounders. A total of 10 patients withdrew from the study and 52 completed the study. The primary and secondary outcomes were measured in the first visit with each participant and then again at the second visit 7 hours (+/- 30 minutes)
after ingesting the concealed medication. The second visit took place within 28 days of the first visit and the participant must have been stable throughout the duration of the study.⁹

The primary outcomes measured were SDMT and PASAT. Secondary outcomes were BDIFS and FSS. There were no significant differences in demographics, prognosis, or baseline scores between the three groups. Only four participants reported nausea, palpitations, and tremor on the amphetamine, while two participants on the placebo reported arm tingling and headaches. There was no mention of participants withdrawing due to any adverse events.⁹

Visual processing speed by SDMT was significantly improved by 5.2 points verses 0.6 points when comparing the 10mg MAS-XR group to the placebo group. PASAT demonstrated a positive trend, but was not significant. There was no significant change in secondary outcome scores. Adverse events were reported and noted throughout the study.⁹

**DISCUSSION**

Cognitive impairment continues to impact the lives of MS patients, yet there is still no recommended medication to improve this debilitating symptom. Both isomers⁶,⁸ as well as mixed amphetamine salts⁹ have showed significant promise through the evidence; however, significant limitations were found including some nonsignificant findings, high report of minor adverse events, and significant baseline differences. Despite these limitations, the benefits of using amphetamines to improve quality of life in MS patients still seem to outweigh the risks.

After careful analysis across all relevant studies, the evidence validates that amphetamines can play a significant role in improving cognitive impairment in MS patients. SDMT scores were consistently measured across all studies in this review. The significant increase in objective scores in SDMT in two out of three studies suggests that visual processing...
speed improves with the use of amphetamines.\textsuperscript{8,9} More improvement was shown in the CVLT2 scores suggesting amphetamines can have an impact on auditory and verbal learning as well.\textsuperscript{6}

The benefits of this review were shown by the improvement of cognitive function, but risks must also be outlined. Each study documented adverse events and reported them for discussion of safety and tolerance. The Morrow & Rosehart study\textsuperscript{9} assessing MAS-XR had the fewest reported adverse events, which is likely due to the lower amounts of each isomer. There were no withdrawals due to side effects. In the Morrow et al (2013) study\textsuperscript{8} assessing LDX, the adverse events were reported to be high in both the LDX group and the placebo group. None of the side effects reported were serious, but a number of participants withdrew because of them. Similarly in the Morrow et al (2009) study\textsuperscript{6} assessing L-amphetamine, the adverse events were reported to be high in both groups and a few patients also withdrew from the study. The intervention groups in both of these studies\textsuperscript{6,8} did have higher rates of events than the placebo group, despite both groups being high. These findings reveal that in the studied doses, the amphetamines are safe for these patients; however, the MAS-XR is the leading choice for type of amphetamine most efficacious and tolerated by MS patients with the least amount of side effects, which is a consistent finding in adult patients with ADHD.\textsuperscript{10}

While these were well controlled and randomized studies graded at a low level, there were limitations that may give hesitation towards applying the hypothesis to a clinical setting. All studies\textsuperscript{6,8,9} fell short with the given duration the patients were taking the intervention, between 1 dose and 14 days on the maximum dose. This limits the ability to assess the long-term implication of the amphetamines in terms of both efficacy and tolerance. There was also no mention or ability to assess the patients building a tolerance to the amphetamines and needing a
higher dose to achieve the desired effects. In the study giving a single dose\(^9\), there were fewer reported adverse events, but this may also be limited by the amount of medication taken and the brief period of time it was impacting the patient. Therefore, the study may not have given an accurate representation of adverse events and is at risk of reporting bias. The Morrow et al (2013) study,\(^8\) revealed a serious limitation due to the significant difference between baseline SDMT scores and BVMTR scores with greater impairment in the LDX group. This could have exaggerated the results of the study in favor of the hypothesis and show inflated cognitive improvement in the intervention group.

All studies\(^6,8,9\) had a similar concern because not a single study gave statistically significant results in all primary outcomes. This is a serious limitation even though each study reveals a significant finding that supported the hypothesis that amphetamines can improve cognitive function in MS patients. Furthermore, there were no significant findings that showed a subjective improvement from the standpoint of the patient. While the objective results show improvement, the question still remains if the amphetamines improve quality of life of the patients in their activities of daily living. Lastly, all three studies reviewed had the same lead author, which may be seen as a limitation with potential for bias; however, this is not counted as a weakness in the evidence due to the author being at the forefront of the research in this field and one of the only researchers currently working on the subject.

Even with convincing evidence, further research is necessary to completely validate the use of amphetamines for cognitive improvement in MS. To apply this research to a clinical setting, there must be more information on how this will impact MS patients with comorbidities and how the medication is tolerated long term. The next step in research is to first achieve
consistent and statistically significant results that show that the amphetamines are tolerated and efficacious over a long duration. Then, to apply the research to a broader range of patients, study how the medication is tolerated and effects MS patients with common comorbidities, such as depression. Quite possibly the most important research to be done is how amphetamines can impact the quality of life in these patients. Therefore, finding a better method for patients to express their self-rating on whether or not the medication improves function and daily life is crucial to applying the research in a clinical setting.

CONCLUSION

The results of this systematic review demonstrate that amphetamines may improve cognitive function in patients with MS. While there are limitations to the current efforts, there is enough evidence to support that this is a topic worthy of further research. For patients with reliable follow up for monitoring, the evidence is strong enough to support consideration of the use of MAS-XR in MS patients with complaints of cognitive deficits. There are options for MS patients to treat depression, pain, and fatigue, but no treatment recommendations exist for cognitive function except amphetamines. This is a good option and, so far, the only option for patients to regain some mental capacity and function. If research continues, amphetamines may become the mainstay of treatment of cognitive function in MS and further research will find ways to make its use safer with less adverse effects for patients.
REFERENCES


### Table I. Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Upgrade Criteria</th>
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<td>Not Serious</td>
<td>Serious</td>
<td>Unlikely</td>
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<td>Morrow et al, 2012</td>
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<td>Not Serious</td>
<td>Not Serious</td>
<td>Serious(^a)</td>
<td>Unlikely</td>
<td>None</td>
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<tr>
<td>Morrow &amp; Rosehart</td>
<td>RCT</td>
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<td>Not Serious</td>
<td>Not Serious</td>
<td>Serious(^a)</td>
<td>Unlikely</td>
<td>None</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

\(^a\) Primary outcomes were not all statistically significant for any of the studies included.

\(^b\) There is a significant difference in the baseline objective measurements for the primary outcomes between the intervention and control group.

\(^c\) This is a single-dose study did not address the potential for long term affects and adverse events. Potential Reporting bias due to minimal disclosure and analysis of adverse events.
<table>
<thead>
<tr>
<th>Test</th>
<th>Morrow et al (2009)(^7)</th>
<th>Morrow et al (2013)(^8)</th>
<th>Morrow &amp; Rosehart(^6)</th>
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<tr>
<td>SDMT</td>
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<td>PASAT</td>
<td>N</td>
<td>Positive</td>
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<tr>
<td>PSAT</td>
<td>Y</td>
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<td>BVMT-R – TL</td>
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<tr>
<td>BVMT-R – DR</td>
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</table>

Y, yes
N, no
--, not an outcome of the study