Pioglitazone and Alzheimers Disease, a Possible Treatment and Preventative Modality

Jeffrey C. Otis

Recommended Citation
Otis, Jeffrey C., "Pioglitazone and Alzheimers Disease, a Possible Treatment and Preventative Modality" (2016). School of Physician Assistant Studies. 597.
https://commons.pacificu.edu/pa/597
Pioglitazone and Alzheimers Disease, a Possible Treatment and Preventative Modality

Abstract

**Background:** Alzheimers disease is common and debilitating, and diabetes is a widely documented risk factor for the development of Alzheimers disease. Given that Alzheimers disease and diabetes are two extremely common and comorbid conditions in geriatric populations that greatly affect quality of life, it follows that treatment and prevention of both pathologies be exhaustively investigated. This is especially evident, as there is no existing medication that prevents or reverses the pathogenesis of Alzheimers disease. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonists of the thiazolidinedione drug class, acts by up-regulating gene expression cell receptors that improve insulin sensitivity at target tissue. This drug also has the salutary effect of improving patient lipid profiles and acting as an anti-inflammatory agent. Research is evolving that suggests that pioglitazone may play a role in preventing the onset of Alzheimers disease in non-insulin dependent diabetic patients. Moreover, it has also been identified as possibly improving cognition in patients with existing mild Alzheimers disease. The purpose this systematic review is to revisit research that has been completed on pioglitazone regarding its efficacy treating mild cognitive impairment caused by Alzheimers disease as well as its possible role in preventing the onset of Alzheimers disease in diabetic patients.

**Method:** An exhaustive search using MEDLINE-Ovid, Web of Science, and Google Scholar was performed using keywords *pioglitazone* and *dementia*. Studies found were screened with eligibility criteria and analyzed for quality with GRADE. Clinical trials included two pilot, randomized control trials published in 2011 measuring pioglitazone's use to treat mild cognitive impairment caused by Alzheimers disease. A retrospective observational study measuring pioglitazone's preventative effect delaying or preventing the onset of Alzheimers disease was also included; this study has not yet been published, but has been accepted for publication and undergone full peer review.

**Results:** Three studies were included in this systematic review, meeting the eligibility criteria. One RCT looked at 42 patients with NIDDM and mild Alzheimers, showing statistically significant improvement in cognitive function with six months of treatment with pioglitazone. Another RCT looked at 28 patients without diabetes and with mild Alzheimers disease that found no significant improvement in cognition with 18 months of treatment with pioglitazone. Finally, a retrospective observational study demonstrated a 47% risk reduction in the development of Alzheimers disease when patients were treated with pioglitazone for greater than or equal to 8 quartiles (when compared to diabetics not receiving pioglitazone).

**Conclusion:** It is thought that pioglitazone may improve cognition and delay the onset of Alzheimers due to its multiple positive benefits including increasing insulin sensitivity, improving lipid profiles, and acting as an anti-inflammatory agent. While the quality of evidence that is currently available is not enough to suggest the use of pioglitazone to treat mild cognitive impairment caused by Alzheimers disease, there is compelling data to suggest its use as a preventative modality possibly delaying the onset of Alzheimers disease in diabetic patients. This is an evolving area of research, and larger, double-blinded randomized control trials are needed to elucidate pioglitazone's efficacy. If found to be efficacious, pioglitazone, a drug that is widely available and relatively safe to take, could help to uncouple the pathogenesis of two major pervasive and life altering disease processes: diabetes and Alzheimers disease.

**Degree Type**

Capstone Project
Degree Name
Master of Science in Physician Assistant Studies

Keywords
Pioglitazone, dementia, Alzheimers, diabetes mellitus, thiazolidinedione

Subject Categories
Medicine and Health Sciences

This capstone project is available at CommonKnowledge: https://commons.pacificu.edu/pa/597
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Pioglitazone and Alzheimer’s Disease, a Possible Treatment and Preventative Modality

Jeffrey Otis

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 12, 2016

Faculty Advisor: Brent Norris, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Jeffrey Otis is from Minneapolis Minnesota. He pursued his Bachelor of Arts degree from Grinnell College in Grinnell Iowa studying Biology. His clinical background is divided between emergency medicine as an emergency room medical scribe, and women’s health at a non-profit community center as a health educator and clinic assistant. As a future physician assistant, Jeffrey hopes to combine his interest in serving the underserved with his interest in providing excellent patient education.
Abstract

Background: Alzheimer's disease is common and debilitating, and diabetes is a widely documented risk factor for the development of Alzheimer's disease. Given that Alzheimer's disease and diabetes are two extremely common and comorbid conditions in geriatric populations that greatly affect quality of life, it follows that treatment and prevention of both pathologies be exhaustively investigated. This is especially evident, as there is no existing medication that prevents or reverses the pathogenesis of Alzheimer's disease. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonists of the thiazolidinedione drug class, acts by up-regulating gene expression cell receptors that improve insulin sensitivity at target tissue. This drug also has the salutary effect of improving patient lipid profiles and acting as an anti-inflammatory agent. Research is evolving that suggests that pioglitazone may play a role in preventing the onset of Alzheimer's disease in non-insulin dependent diabetic patients. Moreover, it has also been identified as possibly improving cognition in patients with existing mild Alzheimer's disease. The purpose this systematic review is to revisit research that has been completed on pioglitazone regarding its efficacy treating mild cognitive impairment caused by Alzheimer's disease as well as its possible role in preventing the onset of Alzheimer's disease in diabetic patients.

Method: An exhaustive search using MEDLINE-Ovid, Web of Science, and Google Scholar was performed using keywords pioglitazone and dementia. Studies found were screened with eligibility criteria and analyzed for quality with GRADE. Clinical trials included two pilot, randomized control trials published in 2011 measuring pioglitazone’s use to treat mild cognitive impairment caused by Alzheimer's disease. A retrospective observational study measuring pioglitazone’s preventative effect delaying or preventing the onset of Alzheimer's disease was also included; this study has not yet been published, but has been accepted for publication and undergone full peer review.

Results: Three studies were included in this systematic review, meeting the eligibility criteria. One RCT looked at 42 patients with NIDDM and mild Alzheimer's, showing statistically significant improvement in cognitive function with six months of treatment with pioglitazone. Another RCT looked at 28 patients without diabetes and with mild Alzheimer's disease that found no significant improvement in cognition with 18 months of treatment with pioglitazone. Finally, a retrospective observational study demonstrated a 47% risk reduction in the development of Alzheimer's disease when patients were treated with pioglitazone for greater than or equal to 8 quartiles (when compared to diabetics not receiving pioglitazone).

Conclusion: It is thought that pioglitazone may improve cognition and delay the onset of Alzheimer's due to its multiple positive benefits including increasing insulin sensitivity, improving lipid profiles, and acting as an anti-inflammatory agent. While the quality of evidence that is currently available is not enough to suggest the use of pioglitazone to treat mild cognitive impairment caused by Alzheimer's disease, there is compelling data to suggest its use as a preventative modality possibly delaying the onset of Alzheimer's disease in diabetic patients. This is an evolving area of research, and larger, double-blinded randomized control trials are needed to elucidate pioglitazone’s efficacy. If found to be efficacious, pioglitazone, a drug that is widely available and relatively safe to take, could help to uncouple the pathogenesis of two major pervasive and life altering disease processes: diabetes and Alzheimer's disease.

Keywords: Pioglitazone, dementia
## Table of Contents

- Biography .................................................................................................................. 2
- Abstract ...................................................................................................................... 3
- Table of Contents ....................................................................................................... 4
- List of Tables ............................................................................................................... 5
- List of Abbreviations .................................................................................................. 5
- Background ................................................................................................................ 6
- Methods ..................................................................................................................... 7
- Results ....................................................................................................................... 8
- Discussion .................................................................................................................. 13
- Conclusion .................................................................................................................. 16
- References .................................................................................................................. 17
- Table 1 ....................................................................................................................... 19
- Table 2 ....................................................................................................................... 20
- Table 3 ....................................................................................................................... 21
List of Tables

Table 1: Characteristics of Reviewed Studies and GRADE profile
Table 2: A summary of measured cognitive changes in Sato et al\textsuperscript{7} and Geldmacher et al\textsuperscript{8}
Table 3: A summary of findings from Heneka et al\textsuperscript{9} study

List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Alzheimers disease</td>
</tr>
<tr>
<td>ADAS-COG</td>
<td>Alzheimers Disease Assessment Scale-Cognitive Subscale</td>
</tr>
<tr>
<td>AOK</td>
<td>Allgemeine Ortskrankenkassen</td>
</tr>
<tr>
<td>CDR</td>
<td>Clinical Dementia Rating</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of recommendations, assessment, development, and evaluations</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-mental state exam</td>
</tr>
<tr>
<td>NIDDM</td>
<td>Non-insulin dependent diabetes mellitus</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>rCBF</td>
<td>Cerebral profusion</td>
</tr>
<tr>
<td>RR</td>
<td>Risk reduction</td>
</tr>
<tr>
<td>RRR</td>
<td>Relative risk reduction</td>
</tr>
<tr>
<td>WMS-R1</td>
<td>Wechsler Memory Scale-Revised logical memory 1 (WMS-R)</td>
</tr>
</tbody>
</table>
Pioglitazone and Alzheimer’s Disease, a Possible Treatment and Preventative Modality

BACKGROUND

The Alzheimer’s Association reported in 2014 that one in nine people age 65 and older has Alzheimer’s disease.¹ Cheng et al² demonstrated in a large meta-analysis that across multiple studies, diabetes mellitus increased the risk for developing any type of dementia including mild cognitive impairment and Alzheimer’s disease (AD). Specifically, there has been evidence that suggests insulin deregulation and resistance may play a role in the multifactorial nature of dementia. Insulin resistance and hyperglycemia cause oxidative stress, worsen lipid profiles, and recruit pro-inflammatory markers to brain tissue resulting in further damage that encourage the pathogenesis of Alzheimer’s.³ Thus, diabetes is widely recognized as a significant risk factor for the development of dementia.

Given that Alzheimer’s disease and diabetes are two extremely common and comorbid conditions in the geriatric population affecting quality of life, it follows that treatment and prevention of both pathologies be exhaustively investigated. There exist several medications that improve cognition in patients with Alzheimer’s disease and dementia such as cholinesterase inhibitors (e.g., donepezil and galantamine), and N-methyl-D-aspartate antagonists (e.g., memantine); however, no medication exists that slows or prevents the progression of the disease process.¹³ As such, prevention and treatment of Alzheimer’s and dementia is an evolving and necessary field of study, including management of risk factors and comorbid conditions such as diabetes. However, it has been found that tight control of serum glucose with metformin alone in non-insulin dependent diabetics may actually increased patient risk for development of Alzheimer’s disease.⁴
In the last decade, research has been done that suggests that the thiazolidinedione drug class (e.g., rosiglitazone and pioglitazone) may delay onset and improve cognition in patients with Alzheimers due to its action improving insulin sensitivity on brain tissue, its salutary effects improving patient lipid-profiles, and acting as an anti-inflammatory agent. Initial research focused on rosiglitazone, which showed mixed results as a treatment modality; however, rosiglitazone has since been given a Food and Drug Association (FDA) black box warning for myocardial infarction and thus is less readily prescribed – and for this reason, it is less likely to be studied.5

Because rosiglitazone received this significant black box warning, the research focus has shifted to pioglitazone. In a mouse model study, Searcy et al6 found that after four months of treatment with pioglitazone, mice had improved learning, reduced serum cholesterol levels, decreased hippocampal amyloid-beta and tau deposits, and improved memory plasticity. The purpose of this systematic review is to revisit research that has been completed on pioglitazone regarding its efficacy when used to treat mild Alzheimers as well as its potential preventative effects postponing the onset of mild cognitive impairment (MCI) due to AD.

METHODS

An exhaustive literature search using MEDLINE-Ovid, Web of Science, and Google Scholar was conducted. The following search terms were used: pioglitazone, thiazolidinedione, dementia, and Alzheimers disease. Terms were then narrowed to pioglitazone and dementia. Additionally, the bibliographies of relevant articles were used to bring forth any other studies and background information. Included were human studies, studies written in English, studies with relevant primary outcomes, and studies with measurable outcomes. Excluded studies were articles, conferences, and posters that did not provide data regarding treatment effect.
RESULTS

This searching method yielded 40 articles for review. After screening for relevant articles that met the aforementioned eligibility criteria, there were a total of three articles. Articles found were two randomized controlled trials\(^7,^8\) measuring pioglitazone’s use as a treatment for mild cognitive impairment in mild Alzheimer’s disease, and one retrospective observational investigation\(^9\) measuring pioglitazone’s effect as a preventative tool delaying Alzheimer’s disease in diabetic patients. This last study\(^9\) has not yet been published but has been accepted for publication and undergone full peer review. Moreover, a large, double-blind random control trial called the TOMORROW study\(^10\) is currently being conducted by Takeda Development Center Americas, Inc., testing the use of pioglitazone as a preventative measure in delaying the onset of mild cognitive impairment due to Alzheimer’s as well as the efficacy of using genetic markers to predict Alzheimer’s. Included articles were given a GRADE profile (Table 1).

**Sato et al**

In this prospective randomized, open-controlled pilot study\(^7\) published in 2011, Sato et al attempt to measure the efficacy using pioglitazone to improve cognition in non-insulin dependent, type II diabetic patients with a Clinical Dementia Rating score of 0.5-1 (i.e., mild Alzheimer’s disease). The primary outcome relevant to this research paper was improvement on mini-mental state examination (MMSE); Alzheimer’s Disease Assessment Scale-Cognitive Subscale, a Japanese version (ADAS-Jcog); as well as Wechsler Memory Scale – Revised (WMS-R) logical memory I. Cognition was tested at six months of treatment. Several other endpoints were considered at six months of treatment including fasting plasma glucose, fasting immune-reactive insulin (FIRI), and homeostasis model assessment ratio (HOMA-R).
Researchers also measured the effect pioglitazone has on cerebral perfusion (rCBF) measured by SPECT MRA studies.  

The study enrolled 42 eligible patients from the Memory Clinic at Tokyo Medical University Hospital. Included participants were diagnosed with Alzheimer’s disease via National Institute of Neurological and Communicative Disorders and Stroke-The Alzheimer’s Disease and Related Disorders Association criteria and met standard criteria for a diagnosis of diabetes.

Exclusion criteria included evidence of complicating neurological and psychological disorders, including depression and anxiety qualified as causing memory impairment, or use of medications such as neuroleptics, benzodiazepines, and antidepressants. Moreover, significant morbidity (cancer, chronic renal disease, heart failure, or uncontrolled insulin dependent diabetes) was also used as an exclusionary marker. Authors note that patients taking the cholinesterase inhibitor donepezil were included in the study if treatment had been stable for six months prior to the start date of the study and did not fluctuate during the study. Enrolled patients were randomized into prognostically similar groups: treatment with pioglitazone 15-30mg per day (n=21) or control (n=21). Of note, this is an open-label study design and participants were aware of designation to control group, however designation was provided via sealed envelope method for one-sided blinding.

MMSE, ADAS-Jcog, and WMS-R logical memory I scores were recorded at baseline and at six months of treatment by a psychometrist blinded to the clinical data. Researchers found that MMSE, ADAS-Jcog and WMS-R logical memory I scores improved with statistical significance in treatment with pioglitazone group compared to scores recorded in control group. Moreover, ADAS-Jcog scores worsened for control groups over the duration of the study (Table 2). Interestingly, researchers found that rCBF deficits in the parietal lobe were improved after six
months treatment with pioglitazone; perfusion deficits in the posterior cortices and parietal lobe are often used as a radiological marker for the diagnosis of Alzheimer's disease. There was no loss to follow up during this clinical trial.  

Due to the limitations of this study, and the nature of the measuring neurophysiological performance without a clear division or binary between no change and cognition improvement, an event rate was not calculated. Moreover, researchers only included the average change in neuropsychological scores of the entire treatment (n=21) and control group (n=21) without including raw data to provide further calculations such as NNT, RR, RRR, etc. Sato et al acknowledge that the study has inherent flaws including incomplete blinding and small sample size. However, because cognitive function was found to be significantly improved by pioglitazone use in the treatment group, this study necessitates that a larger, double-blinded RCT study be completed with similar endpoints measured.  

Geldmacher et al  

In this double-blinded, placebo controlled pilot clinical trial published in 2011, Geldmacher et al investigate the safety of using pioglitazone in treatment of patients with Alzheimer's disease. As a secondary endpoint, researchers also attempted to measure the efficacy of pioglitazone when used as treatment for mild Alzheimer's via assessment with Clinical Dementia Rating (CDR), ADAS-cog, Neuropsychiatric Inventory (NPI), Alzheimer's Disease Functional Assessment and Change Score, and Nurses’ Observation Scale for Geriatric Patients. For the purpose of this paper, ADAS-cog, CDR, and NPI scores are considered over other measurements.  

Twenty-nine participants were enrolled in this study that met the criteria established by the authors. Included participants were non-diabetic patients with a probable Alzheimer's disease
diagnosed via National Institute of Neurological and communicative Disorders and Stroke-The Alzheimers Disease and Related Disorders Association criteria. Other inclusion criteria included a baseline MMSE score between 12-26 and a CDR score of 1-2 (i.e., patients mild Alzheimers disease). Patients with significant morbidity such as heart failure, diabetes mellitus requiring oral treatment or insulin treatment, as well as patients with neuropsychological disorders impacting baseline cognition, were excluded from the study.

For this 18-month trial, enrolled patients were randomized and divided into two groups: treatment and control. Treatment group (n=14) received 15 mg pioglitazone titrated to 45 mg over the first three weeks of the study. Control group (n=14) received a matched placebo. All participants were also instructed to discontinue use of all vitamin supplementation including over the counter, and were given 200-IU vitamin E capsules to take daily due to known interaction between vitamin E and PPAR-gamma. Participants were evaluated every three months for a total of 18 months for health status as well as neuropsychological status. Researchers measured metabolic markers such as blood glucose, hemoglobin A1c, and liver function tests as well.\(^8\)

Regarding neuropsychological function, researchers found that there was no significant treatment effect (Table 2). However, Geldmacher et al acknowledge that it was predicted there would be no significant treatment effect due to small sample size. Moreover, the authors acknowledge that despite randomization, the average age of the treatment group was 74.9 years old compared to the average control age of 67.0 years old, a prognostic difference that may obscure any treatment effect. Of the 29 participants, a total of four patients were lost to follow up: two from treatment, and two from control group. Of note, the use of pioglitazone was well tolerated by participants with the exclusion of mild edema that did not prevent participants from
continuing on in the study. Mild edema was found in four treatment participants, versus zero suffering edema in the control group.

Heneka et al

Heneka et al\textsuperscript{9} conducted a large-scale, retrospective observational analysis using accumulated data from 2004-2010 examining the association between pioglitazone and dementia. Specifically, researchers were expecting to find a decrease in incidence of dementia in diabetic patients taking pioglitazone compared to diabetic patients not taking pioglitazone. The authors examined the impact of several other covariates on dementia incidence as well including cerebrovascular disease, hypertension, ischemic heart disease, atrial fibrillation, and hypercholesterolemia.\textsuperscript{9}

Observational data from 2004-2010 was collected from Germany’s largest public health insurance group Allgemeine Ortskrankenkassen (AOK). Data was screened for sex, age, ICD-10 diagnosis codes, and filled prescription medications. Heneka et al\textsuperscript{9} included all patients that were 60 years or old in 2004, and of that pool, all that had a new diagnosis of dementia from 2006-2010. Dementia incidence was examined using ICD-10 codes as well as further validation of diagnosis to eliminate false positive diagnoses. Of the original pool, 13 177 patients developed dementia during the period of analysis and were found to have a valid diagnosis through rigorous analysis.\textsuperscript{9}

Those that developed dementia were further subdivided into groups distinguished by the presence of diabetes, diabetes but no pioglitazone use, diabetes and pioglitazone use for less than eight quarters of a year, and having diabetes and receiving pioglitazone for equal to or greater than eight quarters of a year. Moreover, authors note that they corrected for the potentially complicating effects of concomitant use of other diabetes medications, mortality, exit from AOK
insurance use, or significant morbidity by using ICD-10 codes as well as rigorous methodology to exclude false positive diagnoses. Data was compared to findings of non-diabetic patients to measure treatment effect.  

Heneka et al used collected data to extrapolate hazard ratios for observed and predicted rates of dementia, again monitoring the effect of length of treatment (less than or greater than 8 quarters of treatment with pioglitazone). Using hazard ratios, researchers further analyzed the data using a Cox proportional hazard model to examine relative risk of dementia with use of pioglitazone, rosiglitazone, metformin, and the before-mentioned covariates.

Researchers found that treatment with pioglitazone for greater than eight quarters greatly reduced the incidence of dementia in diabetic patients when compared to diabetics that did not receive pioglitazone. Incidence was adjusted to per 1000 person-years; diabetes with pioglitazone treatment for greater than eight quarters had an incidence of 7.41 (CI 4.21 - 13.04) compared to diabetics without treatment with pioglitazone with an incidence of 28.37 (CI 27.61 - 29.15). Relative risk was subdivided into age groups to measure treatment effect (Table 3). Importantly, long-term use of pioglitazone was found to reduce risk of developing dementia in diabetic patients by 47% (RR=0.53) whereas diabetics not receiving pioglitazone treatment had a 23% increase in dementia risk (RR=1.23) (Table 3).

**DISCUSSION**

Animal studies have shown remarkable pharmacological effects using pioglitazone including improved learning, reduced serum cholesterol levels, decreased hippocampal amyloid-beta and tau deposits, and improved memory plasticity. The research that has been done in clinical trials thus far is contradictory in that it has conflicting results; Sato et al found a statistically significant treatment effect whereas Geldmacher et al found no significant treatment
effect. However, this inconsistency may be related to the fact that in the Geldmacher et al. study, there were remarkable prognostic differences between treatment and control groups. Specifically, in this study, the treatment group was much older than control by an average of 7.9 years, and age is known to be the greatest risk factor for development of AD.1 The most compelling evidence exists with the Heneka et al study9, with a relative risk reduction of 47% of the development of AD in patients using pioglitazone for longer than an eighth quartile time span.

What evidence does exist makes it abundantly clear that using pioglitazone for treatment and prevention of Alzheimer's disease is a developing pharmacological option that requires a large, double-blinded clinical random control trial. Synthesizing the above information, there does not currently exist enough evidence to implement using pioglitazone as a treatment for MCI in mild Alzheimer's disease due to significant limitations in quality of what research exists.

As mentioned, there were major limitations in what literature was found. Both available randomized control studies were conducted on small sample sizes (n=42, n=29), and neither study included any raw data regarding patient demographics or individual responses to treatment. Because only the average of the total treatment effect (average change in cognitive function scores) was provided, no further analysis of data could be completed; it is impossible to determine if some individuals experienced a greater treatment effect when compared to others because only the average is provided. Moreover, Sato et al.7 acknowledge that because their study is an open-label control study there is a potential for a placebo effect. Geldmacher et al.8 state that it was expected they would not observe a treatment effect due to the small sample size, noting also that the treatment and control group were not prognostically similar despite randomization. Heneka et al.9 provided a larger scale epidemiological with compelling data.
suggesting that pioglitazone has a very significant impact in delaying the onset of MCI caused by Alzheimers disease in patients with diabetes.

Because there was a statistically significant treatment effect in the Sato et al study, the larger study of the two random control trial studies, and because of the large measured preventative effect measured by Heneka et al, this area of study warrants further analysis and further testing. The TOMORROW study\(^{10}\) is currently underway and may clarify the efficacy of using pioglitazone as a preventative medication for Alzheimers disease – which, coupled with the research provided in this systematic review, may unveil new measures that can be taken to prevent disease.

Pioglitazone is a drug that is readily available and that was widely tolerated throughout the above studies, the primary adverse drug reaction being mild edema that was not significant enough to abscond participants from any studies. While at this stage, the research available may not be enough to suggest wide-scale use for non-diabetic patients, there is not significant harm associated with using pioglitazone that would prevent providers from considering its use concomitantly. Its use with other diabetes medications can tightly control serum glucose level with the possible added benefit of preventing or delaying the onset of Alzheimers disease in this at risk population.\(^1\) As a treatment for mild cognitive impairment caused by Alzheimers disease, not enough is known to suggest pioglitazone’s use.

If pioglitazone were found to be a preventative drug option delaying the onset of Alzheimers disease and improving cognition in MCI Alzheimers patients, it would be a significant breakthrough in the field of Alzheimers disease research. Diabetes is a known risk factor for the development for Alzheimers disease and dementia, and both Alzheimers and diabetes are pervasive and life-altering pathologies that are extremely common. Uncoupling the
pathogenesis of these two diseases would save billions of industry dollars, countless years of life, and improve quality of life.

CONCLUSION

Pioglitazone can be considered as an adjunct therapy in the treatment of NIDDM as it may have the benefit of delaying or preventing the onset of Alzheimers disease. The overall quality of evidence for pioglitazone’s use has significant limitation and is of low quality and with opposing findings, however this is an ongoing area of research and there is currently a large-scale, double-blinded random control trial underway in the TOMORROW study. If found to be efficacious, pioglitazone may be used to uncouple the pathogenesis of two major, pervasive life altering diseases, diabetes and Alzheimers disease. This advancement would be a major breakthrough in Alzheimers disease research.
References


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Study Designs</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Limitation</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Improved Cognition</td>
<td>2</td>
<td>RCT</td>
<td>Serious(^a)</td>
<td>Not Serious</td>
<td>Serious(^b)</td>
</tr>
<tr>
<td>Prevention of AD</td>
<td>1</td>
<td>Retrospective</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTES

- a. Lack of complete blinding in Sato et al\(^7\), prognostic difference between treatment and control groups in Geldmacher et al\(^8\)
- b. Studies had conflicting results
- c. Small sample sizes
- d. Some evidence of a dose-response gradient
Table 2. A summary of measured cognitive changes in Sato et al\textsuperscript{7} and Geldmacher et al\textsuperscript{8}

<table>
<thead>
<tr>
<th></th>
<th>TREATMENT (n=21)</th>
<th>CONTROL (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (SD)</td>
<td>6 months treatment (SD)</td>
</tr>
<tr>
<td>Sato et al\textsuperscript{7}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>22.1(3.5)</td>
<td>23.1(4.1)</td>
</tr>
<tr>
<td>ADAS-Jcog</td>
<td>15.5(5.9)</td>
<td>14.2(6.5)</td>
</tr>
<tr>
<td>WMS-LM1</td>
<td>6.5(4.1)</td>
<td>7.8(4.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geldmacher et al\textsuperscript{8}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>21.79(7.3)</td>
<td>27.25(11.92)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>10.43(9.68)</td>
<td>6.75(8.55)</td>
</tr>
<tr>
<td>NPI</td>
<td>6.44(2.13)</td>
<td>8.92(4.15)</td>
</tr>
</tbody>
</table>
Table 3. A summary of findings from Heneka et al's study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Person-years (n=633,418)</th>
<th>Subjects with dementia (n=13,177)</th>
<th>Dementia incidence rate per 1000 person-years</th>
</tr>
</thead>
</table>
|          | Number (percent)         | Number (percent)                 | Rate                                          | 95% Confidence Interval  
| No diabetes | 443,559 (70.0)        | 7,845 (59.5)                      | 17.69                                         | 17.30 - 18.08                
| Diabetes without PIO* | 185,864 (29.3)       | 5,273 (40.0)                      | 28.37                                         | 27.61 - 29.15                
| Diabetes and PIO <8 qrts | 2,375 (0.4)         | 47 (0.4)                          | 19.79                                         | 14.87 – 26.34                
| Diabetes and PIO >=8 qrts | 1,620 (0.3)         | 12 (0.1)                          | 7.41                                          | 4.21 - 13.04                

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 Age 60+</th>
<th>Model 2 Age 60-69</th>
<th>Model 3 Age 70-79</th>
<th>Model 4 Age 80+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Diabetes and no PIO</td>
<td>1.23</td>
<td>1.19-1.28</td>
<td>1.61</td>
<td>1.37-1.88</td>
</tr>
<tr>
<td>Diabetes and PIO &lt;8</td>
<td>1.16</td>
<td>0.87-1.55</td>
<td>1.13</td>
<td>0.46-2.80</td>
</tr>
<tr>
<td>PIO &gt;=8</td>
<td>0.53</td>
<td>0.30-0.94</td>
<td>0.41</td>
<td>0.06-2.92</td>
</tr>
</tbody>
</table>

*PIO = pioglitazone