Major depressive disorder (MDD) is characterized as a disabling psychiatric disorder, presenting with a loss of pleasure and interest in activities that normally bring satisfaction and enjoyment. MDD is a common disorder, roughly occurring at least once in the lifetime of 16.2% of US adults (32.6-35.1 million people), and at least once in the past year of 6.6% of US adults (13.1-14.2 million people). Studies show that being female, middle aged, divorced, low income, or Native American increase the risk of depression. Approximately 80% of depressed people are not currently treated and for those that are, antidepressants only work for 55-65% of them. In a group of studies evaluated by the FDA, placebos were approximately 80% as effective as the six leading antidepressant medications.

Antidepressants work by attempting to correct a misbalance of neurotransmitters in the brain. Low levels of serotonin (5-HT) and norepinephrine (NE) can cause depressive symptoms and the correction of these deficiencies has been associated with an improvement of mood. Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) are a newer class of antidepressants that work on both neurotransmitters believed to play a major role in causing depression.

Desvenlafaxine, by Wyeth Pharmaceuticals, Inc., is the third drug in the SNRI class and is the metabolite of venlafaxine. Desvenlafaxine was approved by the FDA in February of 2008, and is expected to be distributed in the second quarter of 2008. The only FDA approved indication for desvenlafaxine is for the treatment of MDD. Desvenlafaxine is also being investigated as the first non-hormonal treatment for vasomotor symptoms attributed to menopause; however, that is not a currently approved indication.

The objective of this article is to review the pharmacology, pharmacokinetics, dosing, and toxicity of desvenlafaxine. In addition, a summary of clinical trials will be discussed.

Pharmacology and Pharmacokinetics

The mechanism of action of desvenlafaxine is through selective blocking of the reuptake of serotonin and norepinephrine. This increases the levels of both neurotransmitters in the synapse which is thought to be beneficial in depressed individuals.

Table 1 outlines the pharmacokinetics of desvenlafaxine. As a once daily dose, the pharmacokinetics are linear and dose proportional from 100 mg-600 mg per day. High fat meals increase the maximum concentration ($C_{\text{max}}$) by 16% but do not affect Area under the Curve (AUC). This implies that desvenlafaxine (PRISTIQ®): A SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITOR
Venlafaxine may be taken with or without food. The main route of metabolism is through conjugation mediated by UDP-glucuronosyltransferase (UGT) isoforms, and through a minor pathway of oxidative metabolism using the CYP3A4 enzyme. Approximately 45% is excreted unchanged in the urine and 19% is excreted as the glucuronide metabolite. Maximum concentration and AUC increase by 32% and 55%, respectively, in patients older than 75 years of age when compared to patients 18 to 45 years of age. Dosing adjustments might be necessary to avoid adverse effects in this particular population.

The pharmacokinetic profile of patients with hepatic insufficiency changes significantly; however, the clinical significance is minimal. AUC increases 35% in patients with severe hepatic impairment and clearance is decreased by 36%. The half life \( t_{1/2} \) increases by 40% in these same patients. Adjusting the initial dose of desvenlafaxine is not needed, but careful monitoring of these patients is recommended.

Patients renal function should be assessed prior to beginning desvenlafaxine. According to the prescribing information, elimination is significantly correlated with creatinine clearance (CrCl). The AUC increases by 42%, 56%, and 116%, in patients with mild, moderate and end stage renal disease (ESRD). The \( t_{1/2} \) of desvenlafaxine was increased to 15.5 hours and 22.8 hours for moderate and end stage renal disease. It is recommended that patients with significant renal disease be dosed every other day with desvenlafaxine.

### Clinical Trials

Liebowitz et al. performed a placebo-controlled, randomized, double-blind trial, using a dose titration of desvenlafaxine. Patients were treated in an outpatient setting for major depressive disorder based on DSM-IV criteria. The primary outcome measure was an improvement in the 17-item Hamilton Rating Scale for Depression at final evaluation. Secondary measures evaluated various other depression measurement tools such as Montgomery-Asberg Depression Rating Scale (MADRS). The authors concluded there was no significant difference between desvenlafaxine and placebo based on the primary endpoint. However, there was a significant difference \( p=0.047 \) between desvenlafaxine vs placebo with the MADRS. The rate of adverse effects for desvenlafaxine was twice the rate noted with placebo (Table 2).

In a similar study performed by Wyeth as part of their phase 3 study program, desvenlafaxine was used at twice the dose as the Liebowitz study. The authors found an adjusted mean change from baseline in the Hamilton Rating Scale for Depression (HAM-D) total score which was significantly greater for both 200 mg \( p=0.002 \) and 400 mg \( p=0.008 \) doses of desvenlafaxine vs placebo. This phase 3 clinical trial also recorded adverse effects that occurred in at least ten percent of patients, which was twice the rate of placebo.

The most complete study was performed by Demartinis et al. where a dose titration of desvenlafaxine was compared to placebo in 461 patients for eight weeks. With nearly equivalent participants in each arm of the study (100 mg/day, 200 mg/day, 400 mg/day, and placebo) there was a significant improvement in HAM-D, Clinical Global Impressions-Improvement Scale (CGI-I) and the Clinical Global Impressions- Severity Scale (CGI-S) score for nearly all doses of desvenlafaxine when compared to placebo. The HAM-D scores for the desvenlafaxine 100 mg/day and 400 mg/day arms were 12.75 and 12.50 respectively, which were both significantly lower than the HAM-D score for placebo of 15.31 \( p = 0.0038, 0.0023 \), respectively. The HAM-D scores for desvenlafaxine 200 mg/day (13.31), was not significant \( p = 0.0764 \). The CGI-I scores were significantly better then placebo for all groups. The CGI-S scores were statistically better then placebo for both the 100 mg/day and 400 mg/day, but not 200 mg/day \( p = 0.017, 0.046, 0.142 \), respectively. The authors concluded desvenlafaxine’s effectiveness for the short-term treatment of MDD.

### Table 1. Pharmacokinetics of desvenlafaxine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2} )</td>
<td>11 h</td>
</tr>
<tr>
<td>( T_{ss} )</td>
<td>4-5 d</td>
</tr>
<tr>
<td>( F )</td>
<td>80%</td>
</tr>
<tr>
<td>( T_P )</td>
<td>7.5 h</td>
</tr>
<tr>
<td>( PB )</td>
<td>30%</td>
</tr>
<tr>
<td>( V_d )</td>
<td>3.4 L/kg</td>
</tr>
</tbody>
</table>

\( F = \) Bioavailability; \( PB = \) Protein binding; \( t_{1/2} = \) Half-life; \( T_P = \) Time to peak plasma concentrations; \( T_{ss} = \) Time to steady state; \( V_d = \) Volume of distribution.

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PharmaNote

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Larger clinical trials that perform head-to-head studies with other antidepressants need to be performed before conclusive evidence based medicine can be applied regarding the role of desvenlafaxine in the long-term treatment of depression.

**Dosing and Administration**

According to the prescribing information, the recommended initial and usual dose is 50 mg by mouth once daily with or without food. The maximum dose is 400 mg daily. Desvenlafaxine is available as a 50 mg and 100 mg extended-release tablet. It is recommended to take the tablets at the same time everyday and do not crush, chew or divide the tablets. Gradual dose reduction is appropriate when using higher then 50 mg daily.

**Toxicity and Safety**

The most immediate concern when beginning any antidepressant medication is the potential increase in the rate of suicidal ideation, especially in adolescents and young adults. This occurs during the early phases of drug therapy and may subside in about 6-8 weeks. Patient’s beginning treatment with desvenlafaxine should be monitored closely for worsening of depressive symptoms including suicidal thoughts and unusual changes in behavior.

Other adverse effects that have been reported in at least 10% of patients using of desvenlafaxine include abdominal pain, asthenia, anorexia, constipation, dry mouth, nausea, vomiting, dizziness, insomnia, nervousness, somnolence, sweating, tremor, vertigo, and abnormal ejaculation. This contrasts to approximately 5% of patients who reported adverse effects from the placebo-treated groups with severity judged as mild-to-moderate. Discontinuation of this medication should be considered if the side effects become severe.

**Cost**

Since desvenlafaxine has not yet been distributed, cost is not available.

**Summary**

Desvenlafaxine has recently been approved by the FDA for the treatment of major depressive

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**Table 2. Clinical Trial Summary Comparing Desvenlafaxine to Placebo**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Desvenlafaxine Dose</th>
<th>η</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liebowitz et al. ⁵</td>
<td>2007</td>
<td>R, DB, PC</td>
<td>100-200 mg/day</td>
<td>234</td>
<td>8 weeks</td>
<td>No SS differences for HAM-D scores. SS differences for MADRS (p = 0.047)</td>
</tr>
<tr>
<td>Garland et al. ⁶</td>
<td>2006</td>
<td>R, DB, PC</td>
<td>200-400 mg/day</td>
<td>375</td>
<td>8 weeks</td>
<td>SS difference in HAM-D score between 200 mg and 400 mg doses vs placebo (p = 0.002, 0.008 respectively)</td>
</tr>
<tr>
<td>DeMartinis et al. ⁷</td>
<td>2007</td>
<td>R, DB, PC</td>
<td>100-400 mg/day</td>
<td>461</td>
<td>8 weeks</td>
<td>HAM-D scores were SS lower for desvenlafaxine vs placebo at 100 mg/day (p = 0.0038), and at 400 mg/day (p = 0.0023), but not SS at 200 mg/day (p = 0.0764). CGI-I scores were SS better then placebo at all doses. CGI-S scores were SS better then placebo at 100 mg/day and 400 mg/day, but not at 200 mg/day. (p = 0.017, 0.046, 0.142, respectively)</td>
</tr>
</tbody>
</table>

CGI-I = Clinical Global Impressions-Improvement Scale; CGI-S = Clinical Global Impressions- Severity Scale; DB= Double Blinded; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberh Depression Rating Scale; η = # of participants; PC = Placebo Controlled; SS = Statistically significant
disorder, and is scheduled for distribution within 8-12 weeks. Desvenlafaxine will provide physicians and patients with another option in the treatment of depression. The pharmacokinetics and pharmacology of desvenlafaxine is comparable to other available SSRI's and SNRI's. Some clinical trials show superiority over placebo while some show non-inferiority. There are no head-to-head trials comparing desvenlafaxine to other active drugs, and therefore conclusions regarding its place in therapy cannot be made. Many of the clinical trials comparing desvenlafaxine to placebo, show beneficial effects at doses between 100 mg and 400 mg daily, yet the recommended dosage is 50 mg daily. Without published efficacy trials of desvenlafaxine 50 mg daily, the lowest effective dose remains unknown. Desvenlafaxine has shown promise in the nonhormonal treatment of vasomotor symptoms attributed to menopause, but the FDA has not currently approved desvenlafaxine for that indication.

References
While there is no cure for Alzheimer's disease, there are several medications on the market designed to help treat the symptoms of the disease. This article will review each of these drugs, its mechanism of action, side effects, cost, and indications for use.

**Tacrine**

Patients with Alzheimer's disease have a gradual decline in memory and their ability to learn, at least in part due to the death of cholinergic neurons. Postmortem exam of the brains of patients with Alzheimer's disease show lesions from the forebrain leading to the hippocampus, the region of the brain involved in memory. The deficit in cholinergic neurotransmission is believed to be related to this decline. By inhibiting cholinesterases, the enzymes responsible for the degradation of acetylcholine, levels of acetylcholine in the CNS will increase, even with a decreased level of cholinergic neurons.

Tacrine was the first cholinesterase inhibitor approved for the treatment of mild-to-moderate Alzheimer's disease in 1993. Tacrine is less selective for neuronal acetylcholinesterase than other, newer agents of the same class and thus exhibits more peripheral cholinergic effects. The most common side effects of tacrine include nausea, vomiting, diarrhea, myalgia, and ataxia. Tacrine can significantly elevate liver enzymes, particularly transaminases. A patient's transaminases must be monitored every other week from at least week 4 to week 16 after starting therapy.

There are mixed reports of tacrine's effectiveness in the treatment of Alzheimer's. One study found 120 mg and 160 mg doses, but not 80 mg, produced a significant (p<0.001) improvement in cognition after 30 weeks of therapy, as measured by the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-cog), a validated scale to assess memory, attention, orientation, and language ability.\(^5\)\(^6\) The same study, among others, found that tacrine therapy produced statistically significant improvements in global function, as measured by the Clinician Interview-Based Impression (CIBI) (p<0.002) and Final Comprehensive Consensus Assessment (FCCA) (p<0.001).\(^7\) Of patients that withdrew from the study due to side effects, the most common reasons were asymptomatic liver transaminase elevation (28%) and gastrointestinal (GI) complaints (16%). A separate study found that after nine months of treatment with tacrine, only 2 of 22 tests of cognition showed any improvement favoring treatment: the color form sorting test (p=0.002) and the similarities test (p=0.04).\(^8\) This study also evaluated caregiver burden and found no improvement after nine months of therapy (p=0.397). This finding is consistent with the results of other studies.\(^9\)

Tacrine is available as Cognex® 10 mg, 20 mg, 30 mg, and 40 mg capsules. The starting dose is 10 mg four times a day, with subsequent 10 mg titrations every 4 weeks based on patient tolerance. Based on a 160 mg (40 mg four times a day) dosing regimen, a one-month supply costs approximately $300. Although the patent expired in September 2007, there are no generic equivalents at this time, likely due to low demand relative to other Alzheimer's disease therapies.

**Donepezil**

Donepezil, the second cholinesterase inhibitor for the treatment of mild-to-moderate Alzheimer's disease, was approved in 1996 under the brand name Aricept®. Unlike tacrine, donepezil has not been associated with hepatotoxicity, possibly due to its unique chemical structure. Its long half-life also allows for once-daily dosing. Furthermore, its enhanced affinity for neuronal acetylcholinesterase relative to tacrine gives it a reduced incidence of peripheral adverse reactions. In 2004, a rapidly disintegrating tablet was approved under the brand name Aricept ODT®. In 2006, both brands received approval for the treatment of severe Alzheimer's disease.

An analysis of several clinical trials showed that donepezil affected both cognition and global function in Alzheimer's patients.\(^10\) A separate analysis showed that these effects varied based on dose after 24 weeks of therapy (p=0.005).\(^11\) A one-year study comparing donepezil and galantamine showed no difference in primary outcome, as measured by the change in Mini-Mental State Exam (MMSE) score after one year of therapy, based upon treatment strategy.\(^12\)\(^13\) Galantamine-treated patients' MMSE score did not differ significantly from baseline (-0.52 ± 0.39 points), while donepezil-treated patients experienced a significant deterioration from baseline (-1.58 ± 0.42 points; p<0.0005). The between-group difference, however, was not statistically significant (p=0.1). The secondary outcome of cognition was measured using the ADAS-cog. While no difference
based on therapy was shown for the overall population, patients with a baseline MMSE score of 12-18 seemed to benefit more with galantamine therapy over donepezil. Patients treated with galantamine experienced a 1.61 ± 0.80 point worsening in MMSE score versus baseline, while patients treated with donepezil experienced a worsening of 4.08 ± 0.84 points (p<0.05). The reasoning behind this subgroup of patients' benefit from galantamine over donepezil is unknown.

The most commonly reported side effects of donepezil include nausea, vomiting, anorexia, diarrhea, fatigue, and muscle cramps. The 5 mg dose is generally well-tolerated, but the incidence of side effects increases with the 10 mg dose, particularly during the upward dose titration phase. Aricept® and Aricept ODT® are available as 5 mg and 10 mg tablets. Upward dose titration should not occur until 4-6 weeks after the start of therapy. Average monthly cost for both strengths averages $185. Patents on donepezil will not expire until 2010.

**Galantamine**

Galantamine is a natural alkaloid originally from the bulbs of the common snowdrop flower, *Galanthus nivalis*. Galantamine tablets and oral solution were approved in 2001 for the treatment of mild-to-moderate Alzheimer's disease under the brand name Reminyl®. This brand name was later changed in the US to Razadyne® to avoid confusion with the diabetes drug Amaryl® (glimepiride). Galantamine tablets require twice daily dosing, as well as a slow titration to therapeutic doses to limit GI side effects. Once-daily Razadyne ER® tablets were approved in 2004 and have similar tolerability and efficacy compared to twice daily galantamine tablets.¹⁴

Like other cholinesterase inhibitors, most of the common side effects of galantamine are related to GI effects. The most frequently reported include nausea, vomiting, diarrhea, dyspepsia, and abdominal pain. These symptoms occur most frequently during the dose-titration phase of therapy and generally resolve with long-term treatment. One study reported that women and those with lower BMI at the start of therapy were more likely to experience nausea and vomiting.¹⁵ Other CNS effects include dizziness, headache, depression, fatigue, and insomnia.

Numerous studies have shown a significant improvement in cognitive function with galantamine therapy for both those with Alzheimer's disease and those with mild cognitive impairment, considered a potential precursor or "transitional state" to Alzheimer's disease.¹⁴,¹⁶ These effects have also been observed in patients suffering from mixed dementia, a combination of both Alzheimer's disease and vascular dementia.¹⁷ Patients treated with galantamine 24 mg/day showed a significant improvement in ADAS-cog score at 6 months (-1.1 points; p<0.05).

Galantamine is available as 4, mg, 8 mg, 12, mg, 16 mg, and 24 mg tablets along with a 4 mg/ml oral solution. The monthly cost is similar for all strengths and averages $200. Patents for galantamine will not expire until December 2008.

**Rivastigmine**

Rivastigmine is a structurally distinct cholinesterase inhibitor for the treatment of mild-to-moderate Alzheimer's that was approved in 2000 under the brand name Exelon®. Rivastigmine displays 10-fold greater inhibition of neuronal acetylcholinesterase compared to its peripheral effects, which may help explain its lower incidence of peripheral cholinergic side effects. Rivastigmine is not metabolized by the cytochrome P450 system and exhibits low protein binding, giving it a low potential for drug interactions. Like other cholinesterase inhibitors, it is recommended to wait four weeks between dose titrations. In July 2007, once-daily transdermal patches were also approved for Alzheimer's treatment.

The most common side effects of rivastigmine include nausea, vomiting, fatigue, diarrhea, and anorexia. To reduce the incidence of side effects, it is recommended to take rivastigmine twice-daily with food. However, at dosages greater than 6 mg daily, the discontinuation rate is still approximately 15%. If a patient ever misses doses for more than several days, it is recommended that they re-start at the lowest dose and titrate slowly back up to avoid side effects. There is evidence to suggest that these effects are lower when using the transdermal system. Multiple studies have shown improvement with rivastigmine therapy based upon the ADAS-cog scale, but these findings have failed to show improvement based on other assessment batteries.¹⁸,¹⁹ In one study, 45% of placebo-treated patients experienced a decline in ADAS-cog score of at least 4 points, generally regarded as the change necessary to
show a clinical difference, after one year of therapy. Only 18.3% of rivastigmine patients experienced the same decline in ADAS-cog score. Patients treated with rivastigmine significantly improved compared to placebo based upon change in MMSE score (p<0.001). Interestingly, two studies using the same protocol showed different results: one showed improvements at all doses, while the other only showed improvement for higher (6 mg to 12 mg daily) doses.

Rivastigmine is available in 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules, as well as 4.6 mg and 9.5 mg transdermal patches. The average monthly cost of therapy is similar for both dosage forms at approximately $200. While generic equivalents of rivastigmine were approved by the FDA in late 2007, the manufacturer successfully defended a patent lawsuit preventing generic equivalents until 2012.

Memantine

Memantine was the first therapy approved for moderate-to-severe Alzheimer's disease in 2003 under the brand name Namenda®. Memantine is a low-affinity non-competitive antagonist of N-methyl-D-aspartic acid (NMDA) receptors, a unique mechanism among Alzheimer's medications. Chronic excitatory activity at NMDA receptors may play a role in the neuronal death that characterizes Alzheimer's.

Table 1. Summary of Clinical Trials for Approved Alzheimer’s Disease Medications

<table>
<thead>
<tr>
<th>Product</th>
<th>Trial</th>
<th>Trial Type</th>
<th>Population studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrine</td>
<td>Knapp et al. 1994⁵</td>
<td>Randomized controlled trial</td>
<td>653 patients at least 50 years old with mild to moderate Alzheimer’s</td>
<td>Significant differences in ADAS-cog at 160mg/day after 30 weeks of study (p &lt; 0.001)</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Passmore et al. 2005¹⁰</td>
<td>Randomized controlled trial</td>
<td>2376 patients with Alzheimer’s disease</td>
<td>Significant differences after 6 weeks that were maintained through 24 weeks of study (p &lt; 0.001)</td>
</tr>
<tr>
<td>Donepezil vs. Galantamine</td>
<td>Wilcock et al. 2003¹²</td>
<td>Randomized, parallel-group trial</td>
<td>182 patients with Alzheimer’s disease</td>
<td>No significant difference in ADAS-cog score vs galantamine after 52 weeks of study</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Brodaty et al. 2005¹⁴</td>
<td>Randomized, controlled trial</td>
<td>971 patients with Alzheimer’s disease</td>
<td>Significant difference in ADAS-cog score after 6 months</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Karaman et al. 2005¹⁹</td>
<td>Randomized, controlled trial</td>
<td>44 patients with advanced moderate Alzheimer’s</td>
<td>Significant differences in Mini-Mental State Exam score after 12 months</td>
</tr>
<tr>
<td>Memantine</td>
<td>Peskind et al. 2006²¹</td>
<td>Randomized, controlled trial</td>
<td>403 patients with mild to moderate Alzheimer’s</td>
<td>Significant differences in ADAS-cog score after 24 weeks of study (p = 0.003)</td>
</tr>
</tbody>
</table>
NMDA receptor activation by glutamate is linked to an influx of intracellular calcium. Excessive calcium in neurons has been shown to cause neuronal damage or cell death. By antagonizing these receptors, it is believed that memantine can slow further neuronal damage. However, glutamate itself is also linked with learning and memory, so appropriate drug therapy ideally should prevent neurotoxicity while also not disrupting the normal physiological actions of glutamate.

Memantine is generally well-tolerated. Side effects include dizziness, confusion, headache, and drowsiness. Memantine produces significant differences using numerous assessment scales including the ADAS-cog (p=0.003) and Severe Impairment Battery (p=0.002), but results have not been as consistent when using the Mini-Mental State Exam (p=0.68). A previous review of clinical trials showed a nonsignificant but consistent decrease in rates of aggression in patients treated with donepezil.

Memantine is available as both 5 mg and 10 mg tablets, as well as a 10 mg/5 mL oral solution. The average monthly cost is approximately $185. The patent for memantine is not set to expire until April 2010.

New Medications

There are a number of new medications in the pipeline for the treatment of Alzheimer’s disease. Many of the drugs currently in clinical trials revolve around altering splicing of APP, either through direct enzyme inhibition or modulation to reduce the formation of certain variants, or through the use of recombinant antibodies to help facilitate their removal from the brains of affected individuals. Bapineuzumab, a monoclonal antibody against Aβ, a product of APP splicing associated with Alzheimer’s disease, is currently in phase III clinical trials. There is also evidence that existing drugs, including statins and etanercept, may be associated with decreased incidence of Alzheimer’s disease. These associations are currently undergoing further study.

Summary

There is no available drug for the treatment of Alzheimer’s disease that alters or slows the underlying progression of the disease. Current practice guidelines from the American Psychiatric Association make no specific recommendations regarding pharmacotherapy, only saying that all currently available agents have evidence supporting their use to treat the cognitive effects of Alzheimer’s disease. However, there is debate as to whether these statistically significant effects translate into clinically meaningful improvement. Currently available medications may offer some symptomatic relief to help ease the burden on caregivers.

References