Change (ADCS-CGIC). Skin irritation and patch adhesions were systematically assessed.

A total of 1,195 patients were randomized to treatment in the double-blind phase, with 970 (81%) completing all 24 weeks; 870 (73%) patients continued into the open-label phase. During the double-blind phase of the study, 83.8% of patients in the 10 cm^2 patch group met the target dose of study drug for ≥8 weeks, compared to 49.5% of the capsule group and 53.1% of the 20mg^2 groups. At the end of the 24-week double-blind phase, the rivastigmine 10 cm^2 patch, 20 cm^2 patch, and capsule treatment groups were significantly better than placebo in ADAS-cog, ADCS-Activities of Daily Living scale, Mini-Mental Status Exam, Trail Making Test A, and ADCS-CGIC (all $p<0.05$), with the exception of the 20 cm^2 patch in the ADCS-CGIC ($p=0.054$). During the open-label phase, 72.6% of participants achieved the target 20 cm^2 patch. At the end of the open-label phase, patients who received rivastigmine in any form during the double-blind treatment period had small declines in the ADAS-cog when compared to baseline (-0.3); those taking placebo in the double-blind phase had a -0.9 change in ADA-cog scores compared to baseline. The most common adverse events associated with rivastigmine were nausea, vomiting, and diarrhea; The 10 cm^2 rivastigmine patch had 3 times fewer nausea and vomiting adverse events compared to rivastigmine capsule (Table 1). The open-label phase adverse events were similar to those reported in the double-blind phase. Patients taking placebo in the double-blind phase had a higher incidence of adverse events when switched directly to the 10 mg^2 patch, suggesting that naïve patients should be titrated using a 5 cm^2 patch. Local skin irritation led to study discontinuation in 2.4% of the 10 cm^2 group and 3.7% in the 20 cm^2 group. The majority of patients (>90%) experienced "none, slight, or mild" skin irritation as their most severe skin reaction during the study. Ninety-six percent (96%) of caregivers in the 10 mg^2 group reported good adhesion over 24 hours, with the patch staying completely on or just starting to lift up at the corners. The conclusion of the study was that transdermal rivastigmine treatment over one year was a convenient, effective, and well-tolerated medication delivery method in patients with AD.

Agomelatine Demonstrates Broad Efficacy in Depression

Agomelatine, a melatonergic agonist and a selective 5-HT2c antagonist, is a novel antidepressant in development for major depressive disorder (MDD). Alan F. Schatzberg, MD, Stanford University, presented a meta-analysis of pooled data from three clinical studies. The objective of the meta-analysis was to determine whether gender or baseline severity of depression had any influence on agomelatine efficacy.

The three studies included in this exercise were an 8-week dose-finding study comparing 1 mg, 5 mg or 25 mg of agomelatine, placebo, and 20 mg paroxetine and two 6-week flexible dose trials of 25-50 mg agomelatine vs placebo. In the flexible dose trials, agomelatine was increased from 25 mg/day to 50 mg/day if there was no change in Hamilton Depression Rating Scale (HAM-D) at week 2**.** Eligible subjects were outpatients aged 18-65 with a DSM-IV diagnosis of MDD, a HAM-D total score ≥22, and a Clinical Global Impression severity rating of ≥4 with no comorbid conditions that would interfere with study participation. Other psychotropic medications that could confound study data were prohibited. The primary efficacy measure in all three studies was the change in total HAM-D score from baseline to the final evaluation. For purposes of the meta-analyses, "less severe" was defined as a HAM-D total score ≤ 27 (the median total baseline score), and "more severe" was defined as a HAM-D total score ≥ 27.

A total of 358 subjects received agomelatine and 363 were treated with placebo. There were no statistically significant demographic differences between treatment groups. In the meta-analysis of overall efficacy, agomelatine was significantly better than placebo ($p<0.001$). Female patients achieved a mean decline in HAM-D score of 13.5 with agomelatine vs an 11.2 decrease with placebo ($p<0.001$); male patients experienced similar reductions (-13.7 with agomelatine vs -9.9 for placebo; $p<0.001$). There were no statistically significant differences in efficacy between men and women.

In terms of efficacy and depression severity, agomelatine was significantly better than placebo in both the less severely depressed patients and

Figure 1. HAM-D Total Score in Patients with Less Severe Depression (HAM-D<=27). Meta-Analysis of 3 Placebo-Controlled Studies.

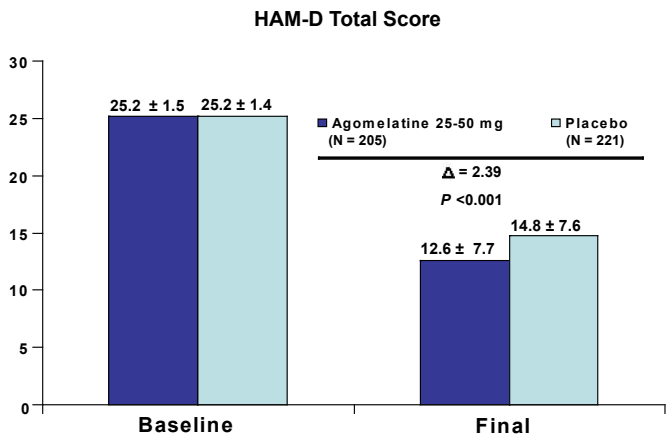
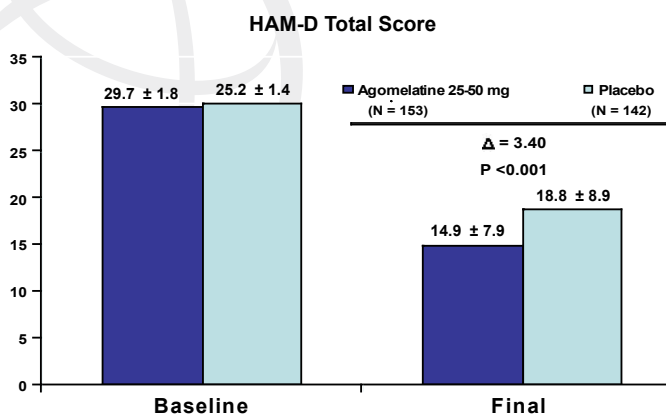


Figure 2. HAM-D Total Score in Patients with More Severe Depression (HAM-D>=27). Meta-Analysis of 3 Placebo-Controlled Studies.



those with greater symptom severity (both p<0.001; Figures 1 and 2). There was no significant difference in efficacy between the two severity groups; however, additional analyses revealed that the subgroup having the greatest difference from placebo were less depressed males, followed by more severely depressed females. This suggests that men and women may respond differently to the medication depending on their symptom severity. Agomelatine efficacy results were recently published online on May 4, 2007 by Pierre and Kasper, in the *International Journal of Neuropsychopharmacology.*

Safety of IM Aripiprazole in Acute Agitation Associated with Dementia

Aripiprazole is an atypical antipsychotic approved for the treatment of schizophrenia. Agitation is a common symptom experienced by patients with dementia, and medications with a rapid onset of action and appropriate tolerability in the elderly are desirable in these situations. This was a multicenter, double-blind, placebo-controlled pilot study to determine the tolerability of intramuscular (IM) aripiprazole in patients with acute agitation associated with dementia and to determine a maximum tolerated dose.

Eligible participants were aged 55-95 years with a diagnosis of Alzheimer's disease, vascular dementia, or mixed dementia. Eligible subjects had to have a PANSS Excited Component (PEC) score between 15 and 32 (inclusive) and a score ≥4 on at least one PEC component (hostility, extreme excitement, poor impulse control, uncooperativeness, tension). The study consisted of a 3 cohort design (Figure 1). Each cohort began with 15 patients, and within each cohort patients were randomized in a 4:1 ratio to receive either active medication or placebo by 2 injections separated by 2 hours. Once an MTD was determined from the 3 cohorts, additional patients were to be enrolled in the MTD cohort until a total of 125 subjects were enrolled. Safety assessments included adverse events, electrocardiograms, vital signs, the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and the Mini-Mental Status Exam (MMSE).

Figure 1. Cohort Study Design.

	Dose	# of injections	Maximum Dose
Cohort 1 15 Patients	2.5 mg aripiprazole or placebo	2	5 mg*
Cohort 2 15 Patients	5 mg aripiprazole or placebo	2	10 mg*
Cohort 3 15 Patients	10 mg aripiprazole or placebo 5 mg apripiprazole or placebo	1 1	15 mg*

*Actual doses:

IM aripiprazole 2.5 mg Cohort: Two injections of 2.475 mg = Maximum dose of 4.95 mg

IM aripiprazole 5 mg Cohort: Two injections of 5.025 mg = Maximum dose of 10.05 mg

IM aripiprazole 15 mg Cohort: One injection of 9.75 mg and one injection of 5.025 mg = Maximum dose of 14.775 mg