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Opioid Antagonist for Olanzapine Weight Gain

In a multinational phase II study, a combined formulation of olanzapine (*Zyprexa*) and the investigational opioid antagonist samidorphan was associated with less weight gain than olanzapine plus placebo.¹

Methods: Study subjects were adults, aged 18–50 years, with established, clinically stable schizophrenia, a body mass index (BMI) of 17–30, and a stable body weight for ≥ 3 months. Participants were required to have had little or no exposure to olanzapine in the prior year. All patients underwent a 1-week open-label olanzapine lead-in to test tolerability and identify those who experienced early weight gain of ≥ 2.2 lbs. Patients continued to receive individually dosed open-label olanzapine throughout the study. For 12 weeks, they also received randomly assigned samidorphan at 5, 10, or 20 mg/day, or placebo. During an additional 12-week extension period, patients either continued to receive their initial samidorphan dose or were switched from placebo to 20 mg/day samidorphan. The study's primary aims were to assess the effects of the combination on antipsychotic efficacy, measured using the Positive and Negative Syndrome Scale (PANSS), and weight gain.

Results: A total of 347 patients were enrolled, 309 completed the olanzapine lead-in, and 300 were randomized and had evaluable results. Study patients had an average age of about 40 years, and about 73% were men. Baseline PANSS scores (mean, 62) and BMI (mean, 25) did not differ between the treatment groups. Early weight gain during the olanzapine lead-in occurred in 65% of patients. A total of 221 patients completed the randomized phase, 218 enrolled in the extension phase, and 187 (85.8%) of those who began the extension phase completed it. Olanzapine plus samidorphan had similar efficacy to olanzapine plus placebo. Average baseline PANSS scores were maintained or decreased slightly during the randomized treatment and extension phases.

During randomized treatment, patients who received olanzapine plus samidorphan gained 37% less weight than those who received olanzapine plus placebo (mean increase, 4.2 lbs vs 6.4 lbs; $p=0.006$). The proportion of patients who gained $\geq 7\%$ of their baseline weight during

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randomized treatment did not differ statistically between treatment groups. However, the risk of gaining $\geq 10\%$ of their initial weight was significantly greater in the olanzapine plus placebo group (odds ratio,* 2.73; $p=0.023$). In patients who experienced early weight gain during the olanzapine run-in, average weight gains during the treatment phase were 4.2 lbs and 8.4 lbs in the samidorphan and placebo groups, respectively. Weight gain of $\geq 10\%$ was 4-times more likely with placebo than with samidorphan. During the extension phase, the mean percent change in body weight remained stable and was similar across all olanzapine plus samidorphan dosages.

The most common adverse events with samidorphan were somnolence, sedation, dizziness, and constipation. The drug had no apparent effects on metabolic parameters (e.g., cholesterol, triglyceride, glucose, and insulin levels), although this was difficult to assess accurately.

Discussion: Antipsychotic-induced weight gain generally has a rapid onset and can occur during the first few weeks of treatment. Starting the trial after 1 week of olanzapine therapy may have masked some of the potential effects of samidorphan. The investigators focused on preventing rather than reversing weight gain since treatment effects are more pronounced before the onset of weight gain. The mitigating effects of samidorphan on weight gain appear to be specific to olanzapine. Although the drug has not been associated with significant weight effects as monotherapy or in patients with other disorders, it was previously shown to have a modest effect on olanzapine-associated weight gain in healthy subjects.² The 10-mg samidorphan dose appeared to have the best balance of efficacy and tolerability and will be further evaluated.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

¹Martin W, Correll C, Weiden P, Jiang Y, et al: Mitigation of olanzapine-induced weight gain with samidorphan, an opioid antagonist: a randomized double-blind phase 2 study in patients with schizophrenia. *American Journal of Psychiatry* 2019; doi 10.1176/appi.ajp.2018.18030280. From Alkermes, Inc., Waltham, MA; and other institutions. **Funded by Alkermes. All study authors disclosed relevant financial relationships with commercial sources, including Alkermes.**

²Silverman B, et al: A randomized, double-blind, placebo-controlled proof-of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. *Schizophrenia Research* 2018; doi 10.1016/j.schres.2017.10.014. See *Psychiatry Drug Alerts* 2018;32 (January):4–5.

*See Reference Guide.

Brexpiprazole: Prolactin Effects

According to an analysis of short- and long-term clinical trials, brexpiprazole (*Rexulti*) has minimal effects on prolactin and causes few prolactin-related adverse events. This observation is consistent with the drug's profile as a partial dopamine D₂ receptor agonist.

Methods: Data were combined by the manufacturer from clinical trials of brexpiprazole in adults with schizophrenia. Short-term trials (n=3) were randomized, double-blind, placebo-controlled, fixed- or flexible-dose studies that included a 14-day screening phase with a washout of previous antipsychotics and 6 weeks of double-blind treatment with brexpiprazole dosages of ≤ 4 mg/day. These studies included 882 patients receiving brexpiprazole and 529 receiving placebo. The open-label extension studies (n=2) were conducted for either 26 or 52 weeks and included >1200 patients, either newly treated or continued from the acute trials at dosages of ≤ 4 mg/day.

Results: Following the 14-day washout in the short-term trials, mean prolactin levels were 21 ng/mL in women and 12 ng/mL in men. By week 6, values in the brexpiprazole group decreased by 1.08 ng/mL in women and by 1.58 ng/mL in men. These decreases were somewhat smaller than those observed in the placebo group. Prolactin increased slightly on average (6.72 ng/mL) in women with initially normal values and decreased (-33.41 ng/mL) in those with values above the upper limit of normal (ULN). Changes were similar but smaller in men.

The 2 fixed-dose studies showed no apparent dose-dependent prolactin increase. In the long-term studies, average increases in prolactin were <1 ng/mL in both genders.

A shift from within the normal range to >3 times ULN occurred in 5.3% of women receiving brexpiprazole in the long-term studies. The proportion of patients with a shift of this magnitude was negligible in women in the acute studies and in men. Of patients with initial levels >1 times ULN, about 25% showed normalization of prolactin in the long-term studies, with little difference between men and women.

Hyperprolactinemia-related adverse events occurred in 16 brexpiprazole-treated patients and 3 placebo-treated patients (1.8% vs 0.6%) in the short-term studies, and in 21 brexpiprazole-treated patients (1.7%) in the extension studies.

Discussion: Antipsychotic-induced hyperprolactinemia is common in patients with schizophrenia and can cause patient distress and impaired quality of life, have negative physical consequences, and affect patient function and treatment adherence. The authors suggest that based on the results in patients in this study who had elevated baseline prolactin levels at baseline, brexpiprazole could potentially be useful as a prolactin-stabilizing or lowering agent in schizophrenia. However, additional research is needed before this use can be recommended.

Ivkovic J, Lindsten A, George V, Eriksson H, et al: Effect of brexpiprazole on prolactin: an analysis of short- and long-term studies in schizophrenia. *Journal of Clinical Psychopharmacology* 2019;39 (January/February):13–19. doi 10.1097/JCP.0000000000000979. From H. Lundbeck, A/S, Valby, Denmark; and Otsuka Pharmaceutical Development & Commercialization, Inc, Princeton, NJ. **Funded by Otsuka Pharmaceutical Development; and H. Lundbeck A/S. All study authors disclosed relevant financial relationships with either H. Lundbeck or Otsuka.**

Antipsychotic Polypharmacy and Psychiatric Rehospitalization

In a population-based cohort study, antipsychotic polypharmacy was more effective than monotherapy at preventing psychiatric rehospitalization in patients with schizophrenia.¹ Specifically, the combination of clozapine and aripiprazole was beneficial.

Methods: The study cohort consisted of all individuals who received inpatient treatment for schizophrenia in Finland in 1972–2014. Relative risks for hospitalization were calculated for periods during which individual patients were receiving no medication, monotherapy with an oral antipsychotic, monotherapy with a long-acting injectable, or polypharmacy with combinations of any of these treatments (29 possible combinations). In order to reduce risk of bias, patients served as their own controls for determining the relative risk of hospitalization for each treatment condition versus a comparator. The primary study outcomes, assessed over a period of ≤20 years, were psychiatric hospitalization and hospitalization for any cause. The results of the analysis were adjusted for factors that varied over time within the individual, such as the order of antipsychotic exposure and use of other psychotropic drugs.

Results: The full cohort comprised >62,000 patients who were followed for a median of 14 years. An incident cohort of patients with first-episode schizophrenia consisted of nearly 9000 patients who were followed from the time of first hospital discharge for a median of 10 years. In the full cohort, 67% of patients used polypharmacy at some time during follow-up, most for ≥90 days. Nearly 60% of patients in each cohort were rehospitalized.

The overall risk of psychiatric rehospitalization was significantly lower during any polypharmacy period than any monotherapy period (hazard ratio,* 0.93; p<0.001; see table, next page). Other adverse outcomes were also reduced with polypharmacy compared with monotherapy; the hazard ratio for all-cause hospitalization was 0.91 (p<0.001), and the hazard ratio for death was 0.76 (p<0.001).

Clozapine was associated with the lowest rate of rehospitalization of any monotherapy. Clozapine–aripiprazole was the only polypharmacy combination superior to clozapine monotherapy (hazard ratio, 0.86; $p < 0.001$). When other drug pairs were compared with the most effective member of the pair, none were statistically superior to the single drug after correcting for multiple comparisons.

Clozapine–aripiprazole was also superior to any other treatment with regard to all-cause hospitalization (hazard ratio, 0.78). The risk of psychiatric rehospitalization, all-cause hospitalization, or death was not reduced significantly by adding any antipsychotic (other than aripiprazole) to clozapine.

Discussion: These results suggest a clinically relevant number needed to treat* of 10–20 to prevent 1 rehospitalization, comparing polypharmacy with monotherapy overall. Because polypharmacy is generally an add-on approach when monotherapy begins to fail, effect sizes for the superiority of polypharmacy may be underestimated. The authors recommend rational antipsychotic polypharmacy based on a combination of agents with different types of receptor profiles.

Editorial.² The superior results for polypharmacy are difficult to explain but could be associated with compensation for partial adherence, by improving adherence, or potentially better tolerability of some drug combinations than monotherapy. Because of limitations inherent to the observational study design, including confounding by indication, the present results must be considered preliminary and clinicians considering add-on treatments should recognize that they are supported by limited evidence.

Treatment	Hazard Ratio
Clozapine and aripiprazole	0.42
Clozapine and olanzapine	0.49
Clozapine monotherapy	0.49
Clozapine and risperidone	0.50
Clozapine and quetiapine	0.52
Any LAI monotherapy	0.56
Olanzapine and quetiapine	0.61
Olanzapine monotherapy	0.64
Aripiprazole and quetiapine	0.65
Olanzapine and risperidone	0.65
Risperidone and quetiapine	0.66
Olanzapine and aripiprazole	0.70
Aripiprazole and any LAI	0.70
Aripiprazole monotherapy	0.74
Risperidone monotherapy	0.75
Aripiprazole and risperidone	0.85
Quetiapine monotherapy	0.93

¹Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, et al: Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2018.4320. From the Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Finnish Ministry of Social Affairs and Health; and other sources. All study authors disclosed potentially relevant financial relationships.**

²Goff D: Can adjunctive pharmacotherapy reduce hospitalization in schizophrenia? Insights from administrative databases [editorial]. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2018.4318. From New York University School of Medicine, New York. **The author disclosed a potentially relevant financial relationship.**

Common Drug Trade Names: aripiprazole—*Abilify*; clozapine—*Clozaril*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*

*See Reference Guide.

Cariprazine for Bipolar Depression

In a phase 3 clinical trial, cariprazine (*Vraylar*) reduced depressive symptoms in patients with bipolar I depression.¹ Treatment did not induce mania, weight gain, or metabolic changes.

Methods: The study, conducted at 72 centers in the U.S. and Europe, enrolled 488 adult outpatients (59% women; mean age, 43 years) with bipolar I disorder and a current depressive episode lasting ≥ 4 weeks. Patients were required to have a score of ≥ 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D), a Clinical Global Impression–Severity* (CGI-S) score of ≥ 4 , and a score of ≤ 12 on the Young Mania Rating Scale (YMRS). After a 1–2 week washout of prior medication, patients were randomly assigned to receive double-blind

cariprazine at a fixed dosage of 1.5 or 3.0 mg/day or placebo for 6 weeks. The primary outcome was change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) score. Rates of response (i.e., $\geq 50\%$ decrease in MADRS score) and remission (i.e., MADRS score ≤ 10) were secondary outcomes.

Results: Cariprazine, at both dosages, resulted in larger decreases in depressive symptoms than placebo (see table), but effect sizes were small. CGI-S scores, a secondary efficacy outcome, also showed larger improvement with cariprazine than placebo. At week 6, response rates were higher with active treatment than with placebo: 48% with 1.5 mg/day cariprazine (odds ratio,* 1.4; $p=ns$) and 52% with 3.0 mg/day cariprazine (odds ratio, 1.7; $p=0.02$). Although the lower dosage did not achieve statistical significance, the placebo response rate was high (40%). Patterns were similar for remission: 23% with placebo, 33% with the lower cariprazine dosage (odds ratio, 1.7; $p=0.03$), and 32% with the higher dosage (odds ratio, 1.7; $p=0.03$).

Clinical Outcomes at Week 6								
	Placebo		1.5 mg/day Cariprazine			3 mg/day Cariprazine		
	Baseline	Week 6	Baseline	Week 6	Significance vs Placebo	Baseline	Week 6	Significance vs Placebo
MADRS Score	30.2	17.6	30.7	15.6	$p=0.03$	31	15.4	$p=0.01$
CGI-S	4.5	3.2	4.5	2.9	$p=ns$	4.5	2.9	$p=ns$

The most common adverse events with cariprazine were nausea, akathisia, dizziness, and sedation, affecting 4–9% of patients. Suicidal ideation occurred in 8–11% of each treatment group. The active drug and placebo had similar effects on body weight and metabolic parameters that were not clinically relevant. Treatment-emergent mania with cariprazine was rare: $<1\%$ of those who received the lower dose and no patients who received the higher dose, compared with 1.3% of the placebo group.

Discussion: Several atypical antipsychotics are currently FDA approved for treatment of bipolar depression. Cariprazine is a second-generation antipsychotic with high affinity for the dopamine D₃ receptor, which may result in positive effects on cognition and mood. It also is a partial agonist of the serotonin 5-HT_{1A} receptor. The results of the present study are consistent with a previously reported phase 2 clinical trial.²

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

¹Earley W, Burgess M, Rezeda L, Dickinson R, et al: Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. *American Journal of Psychiatry* 2019; doi 10.1176/appi.ajp.2018.18070824. From Allergan, Madison, NJ; Gedeon Richter, Budapest, Hungary; and other institutions. **Funded by Allergan; and Gedeon Richter. All study authors disclosed potentially relevant financial relationships with commercial sources, including Allergan or Gedeon Richter for 8 of the 9 authors.**

²Durgam S, et al: An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. *American Journal of Psychiatry* 2016;173 (March):271–281. See *Psychiatry Drug Alerts* 2016;30 (April):27–28.

*See Reference Guide.

Maintenance Ketamine for Resistant Depression

In a group of patients with treatment-resistant depression who experienced relapse following a single ketamine infusion, repeated ketamine infusions produced substantial improvement in symptoms, and weekly maintenance infusions were effective for maintaining response.

Methods: This 3-phase study enrolled patients who had major depressive disorder that was refractory to ≥ 2 medications from different classes and 2 augmentation strategies in the current

episode. Baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores of ≥ 25 were required for entry, and patients remained on stable doses of background medications during the study. The first study phase, designed to evaluate acute efficacy, consisted of a single infusion of randomized, double-blind ketamine or midazolam (the active placebo control) followed ≥ 7 days later by crossover to the alternate agent. Only patients whose MADRS score was $\geq 80\%$ of their baseline rating received the crossover infusion and were eligible for phase 2, which consisted of 3 infusions of open-label ketamine per week for 2 weeks. Patients who completed this phase and achieved response then received 4 weekly maintenance ketamine infusions. The primary study outcome was change from baseline in the MADRS score. Response was defined as a $\geq 50\%$ decrease in MADRS score, and remission as a final score of ≤ 10 .

Results: A total of 43 patients (mean age, 42 years; 56% women) received ≥ 1 randomized infusion and were included in the intent-to-treat sample. The mean baseline MADRS score was 35. At the predetermined phase-1 efficacy endpoint of 24 hours, MADRS scores decreased by a mean of 11 points in the ketamine group, compared with 3 points in the midazolam group ($p < 0.001$). A total of 11 patients (27%) met response criteria after ketamine infusion, and 2 (5%) achieved remission. No patient met response criteria with midazolam.

Of 41 patients who entered the second phase, 39 completed all 6 infusions. On average, participants' MADRS scores decreased by an additional 2 points with each infusion. At the end of this phase, 23 patients (59%) met response criteria, including 9 of the 11 who had experienced response to the single randomized infusion and 14 additional patients. A total of 9 patients (23%) achieved remission. Patients first met response criteria after a median of 3 infusions. The 23 patients who had met response criteria in phase 2 went on to the third phase. There were no further changes in average MADRS scores during weekly ketamine administration, and 21 patients (91%) maintained their response.

The most common adverse effects of ketamine were cardiorespiratory effects, numbness or tingling, dissociation, dizziness, and visual disturbances. These effects were transient and did not result in treatment discontinuation. Patients experienced dissociation significantly more often with ketamine than midazolam ($p < 0.001$).

Discussion: This appears to be the first double-blind crossover trial comparing ketamine with a psychoactive control and the first to evaluate continued responses during repeated infusions. The lack of a placebo response to midazolam attests to the severity and refractoriness of depression in these patients and the reliability of the results. It is noteworthy that patients responded to reintroduction of ketamine following relapse after their first infusion and that the drug's antidepressant effects were cumulative.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Phillips J, Norris S, Talbot J, Birmingham M, et al: Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. *American Journal of Psychiatry* 2019; doi 10.1176/appi.ajp.2018.18070834. From the Royal's Institute of Mental Health Research; and the University of Ottawa, Canada. **Funded by the Canadian Institutes of Health Research. One of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: ketamine—*Ketalar*; midazolam—*Versed*

*See Reference Guide.

Lithium After Ketamine Response

In a randomized trial, lithium continuation therapy following ketamine infusions did not improve outcomes in patients with treatment-resistant depression.

Background: Lithium has previously shown clinical efficacy as an adjuvant to antidepressants or ECT in treatment-resistant depression. Antidepressant effects of ketamine and lithium may

occur via the same mechanisms: inhibition of glycogen synthase kinase-3 (GSK-3) and activation of the mammalian target of rapamycin (mTOR) signaling.

Methods: Study subjects were adults, aged 21–65 years, with a primary diagnosis of major depressive disorder of ≥ 4 weeks' duration and a lifetime history of nonresponse to ≥ 2 antidepressant medications. After screening, all patients received a single infusion of open-label ketamine. Those who demonstrated a $\geq 25\%$ reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score by 24 hours were randomized to double-blind continuation therapy with lithium or placebo. Participants also received additional ketamine infusions on days 7, 9, and 11. The primary study outcome was MADRS score at day 28, approximately 2 weeks after the final ketamine infusion.

Results: The 42 study participants had history of nonresponse to a median of 5 prior antidepressant trials, and 7 patients had also experienced nonresponse with ECT. Following the initial ketamine infusion, 35 patients exhibited at least partial response, and 34 went on to receive ≥ 1 dose of lithium or placebo. At day 28, mean MADRS scores were decreased from 32.5 at baseline to about 25 in both groups. Secondary outcome measures also showed no benefit of lithium over placebo.

Discussion: Ketamine has repeatedly shown rapid and substantial antidepressant effects; however, the benefits of infusion are transient. Although lithium treatment does not appear to be effective, prolonging patients' initial response to ketamine remains an important goal.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Costi S, Soleimani L, Glasgow A, Brallier J, et al: Lithium continuation therapy following ketamine in patients with treatment resistant unipolar depression: a randomized controlled trial. *Neuropsychopharmacology* 2019; doi 10.1038/s41386-019-0365-0. From Icahn School of Medicine at Mount Sinai, New York; and other institutions. **Funded by the Doris Duke Charitable Foundation. Five of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Early Levodopa in Parkinson's

According to the results of a randomized delayed-start trial, early initiation of levodopa plus carbidopa (*Sinemet*) does not slow disease progression in Parkinson's disease.¹ The study results support current practice: treatment that is guided by clinical need.

Background: The possibility that levodopa might modify the course of Parkinson's disease was suggested by the previously published Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study,² which included 40 weeks of randomized placebo-controlled treatment but no delayed-start treatment phase. The present study was designed to replicate many of the features of the ELLDOPA trial, including drug dosage, duration of double-blind treatment, and primary outcome.

Methods: The trial enrolled patients from community and academic hospitals in the Netherlands. Patients had received a diagnosis of Parkinson's disease within the previous 2 years, had taken no antiparkinsonian medication, and were not candidates for immediate symptom relief with levodopa. At baseline, patients were randomly assigned to active treatment with 100 mg levodopa plus 25 mg carbidopa t.i.d. or to placebo. After 40 weeks, all patients received active medication for an additional 40 weeks. Patients in either group who developed a disability requiring medication during the double-blind phase were switched to open-label levodopa-carbidopa. The primary study outcome was change from baseline to week 80 in the Unified Parkinson's Disease Rating Scale (UPDRS). Based on the ELLDOPA trial, the investigators expected to find a between-group difference of 4 points on the 176-point UPDRS, a difference that has been considered clinically relevant.

Results: A total of 445 patients participated in the trial, of whom 417 completed the 80th week. Study participants had a mean age of 65 years and a mean baseline score of 28–29 on the UPDRS. A total of 87 patients in the delayed-start (placebo) group and 24 in the early-start group developed symptoms requiring unblinding and a switch to open-label medication. The primary analysis was completed on an intent-to-treat basis.

After 80 weeks, UPDRS scores did not differ between the early-start and delayed-start groups. Patients in the early-start group improved by a mean of 1 point, and the delayed-start group improved by 2 points, a nonsignificant difference. The early-start group had a larger symptomatic improvement by week 40, but this difference was no longer apparent after both groups received active medication. Secondary outcomes, including symptom progression, disability, cognitive function, depression, and quality of life, also did not differ between the 2 groups at week 80. During randomized treatment, the incidence of nausea was higher in the early-start group (23% vs 14%), but other adverse effects did not differ between the groups.

Discussion: The present results clarify the ambiguous results of the ELLDOPA trial, and suggest that levodopa treatment does not have a disease modifying effect in Parkinson's disease.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

¹Verschuur C, Suwijn S, Boel J, Post B, et al: Randomized delayed-start trial of levodopa in Parkinson's disease. *NEJM* 2019;380 (January 24):315–324. doi 10.1056/NEJMoa1809983. From the University of Amsterdam, the Netherlands; and other institutions. Funded by the Netherlands Organization for Health Research and Development; and other sources. Four of 12 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.

²Fahn S, et al. Levodopa and the progression of Parkinson's disease. *NEJM* 2004;351:2498–2508.

*See Reference Guide.

Reference Guide

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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