

Modafinil Helps Some Cocaine Dependence

BY BRUCE JANCIN
Denver Bureau

VIENNA — Modafinil has now been found to be effective for the treatment of cocaine dependence in two randomized clinical trials, Frank J. Vocci, Ph.D., reported at the annual congress of the European College of Neuropsychopharmacology.

The caveat is that modafinil (Provigil) does not appear to work in individuals

who are both cocaine and alcohol dependent, which is a common situation among cocaine users, said Dr. Vocci, director of the division of pharmacotherapies and medical consequences of drug abuse at the National Institute of Mental Health, Bethesda, Md.

Modafinil is approved by the Food and Drug Administration to promote wakefulness in adults who have excessive daytime sleepiness that is associated with sleep apnea/hypopnea syndrome, nar-

colepsy, or shift work sleep disorder.

The drug has several effects making it of interest as a potential treatment for cocaine dependence, including increases in brain glutamate and gamma amino butyric acid (GABA).

In laboratory studies, modafinil produced clinical effects opposite to those seen in cocaine withdrawal, reduced cocaine self-administration, diminished cocaine-induced euphoria, attenuated the cardiovascular effects of large doses of

cocaine, and showed no untoward effects in combination with the drug of abuse. However, "we still don't have any idea how it's working [as a treatment for cocaine dependence] in terms of mechanisms," Dr. Vocci said.

The first clinical trial to demonstrate efficacy was an 8-week, randomized double-blind study involving 62 treatment-seeking cocaine-dependent patients at the University of Pennsylvania. Participants received a single daily morning dose of 400 mg of

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Important Safety Information (continued)

- A potentially fatal symptom complex, sometimes referred to as Neuroleptic Malignant Syndrome (NMS), has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include immediate discontinuation of antipsychotic drugs
- Tardive dyskinesia (TD), a potentially irreversible syndrome of involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic drugs administered to the patient increase. TD may remit, partially or completely, if antipsychotic treatment is withdrawn. SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of TD
- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing
- Leukopenia, neutropenia, and agranulocytosis (including fatal cases), have been reported temporally related to atypical antipsychotics, including SEROQUEL. Patients with a pre-existing low white blood cell (WBC) count or a history of drug induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy. In these patients, SEROQUEL should be discontinued at the first sign of a decline in WBC absent other causative factors. Patients with neutropenia should be carefully monitored, and SEROQUEL should be discontinued in any patient if the absolute neutrophil count is < 1000/mm³
- Precautions include the risk of seizures, orthostatic hypotension, and cataracts. Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment, or shortly thereafter, and at 6-month intervals during chronic treatment

Please see additional Important Safety Information on adjacent pages, and Brief Summary of Prescribing Information, including Boxed Warnings, at the end of this ad.

modafinil or placebo plus twice-weekly manual-guided cognitive-behavioral therapy (CBT).

The primary outcome—the mean proportion of clean urine samples during the 8 weeks—was 42% in the modafinil group and 24% with placebo. Moreover, 33% of the patients in the modafinil arm achieved 3 consecutive weeks of clean urine samples at some point during the study period, compared with 13% of the controls.

There were, however, no significant differences between the two study groups in any secondary outcome measures, including craving scores and patient-re-

ported cocaine use (*Neuropsychopharmacology* 2005;30:205-11).

In a recently completed, not yet published phase II multicenter double-blind trial, 210 cocaine-dependent patients were randomized to receive modafinil at 200 mg or 400 mg once daily or placebo for 12 weeks. All subjects received manualized CBT once a week. A total of 122 participants completed the study.



The primary outcome measure was the maximum number of consecutive days without cocaine use as determined by urine testing and patient self-report.

In laboratory studies, modafinil produced effects opposite to those seen in cocaine withdrawal.

DR. VOCCI

with modafinil at 400 mg daily.

That is a less robust treatment effect than had been seen in the earlier single-

center trial. But patients with comorbid alcohol dependence were excluded from that earlier trial while roughly 40% in the larger trial were both cocaine and alcohol dependent.

Upon closer analysis of the multicenter trial data, researchers found a statistically significant benefit for modafinil in reducing cocaine use that was confined to the non-alcohol-dependent subgroup, Dr. Vocci said.

Both trials were funded by the National Institute on Drug Abuse.

Despite several decades of research, there remains no approved pharmacotherapy for cocaine dependence. ■



Important Safety Information (continued)

- The most commonly observed adverse events associated with the use of SEROQUEL monotherapy versus placebo in clinical trials for schizophrenia and bipolar disorder were dry mouth (9%-44% vs 3%-13%), sedation (30% vs 8%), somnolence (18%-28% vs 7%-8%), dizziness (11%-18% vs 5%-7%), constipation (8%-10% vs 3%-4%), SGPT increase (5% vs 1%), dyspepsia (5%-7% vs 1%-4%), lethargy (5% vs 2%), and weight gain (5% vs 1%). The most commonly observed adverse events associated with the use of SEROQUEL versus placebo in clinical trials as adjunct therapy with lithium or divalproex in bipolar mania were somnolence (34% vs 9%), dry mouth (19% vs 3%), asthenia (10% vs 4%), constipation (10% vs 5%), abdominal pain (7% vs 3%), postural hypotension (7% vs 2%), pharyngitis (6% vs 3%), and weight gain (6% vs 3%)
- In long-term clinical trials of quetiapine, hyperglycemia (fasting glucose ≥ 126 mg/dL) was observed in 10.7% of patients receiving quetiapine (mean exposure 213 days) vs 4.6% in patients receiving placebo (mean exposure 152 days)

* Data combined from two 8-week, multicenter, randomized, double-blind, placebo-controlled, monotherapy bipolar depression trials. SEROQUEL (300 mg/day; n=327) showed significant improvement from baseline in Montgomery-Asberg Depression Rating Scale total score at Week 1 continuing through Week 8 vs placebo (n=330; P values ≤ 0.0001).

† Data combined from two 12-week, multicenter, randomized, double-blind, placebo-controlled, monotherapy mania trials. SEROQUEL (n=208) showed significant improvement from baseline in Young Mania Rating Scale (YMRS) total score at Day 4 continuing through Day 84 vs placebo (n=195; P values ≤ 0.05).

‡ In pivotal mania trials, the average dose in responders (patients with $\geq 50\%$ improvement in YMRS total score) was 600 mg/day.

§ Twice daily.

References: 1. Data on file, AstraZeneca Pharmaceuticals LP, DA-SER-51. 2. Prescribing Information for SEROQUEL. 3. Calabrese JR, Keck PE, Macfadden W, et al. *Am J Psychiatry*. 2005;162:1351-1360. 4. Thase ME, Macfadden W, Weisler RH, et al, for the BOLDER II Study Group. *J Clin Psychopharmacol*. 2006;26:600-609. 5. Endicott J, Rajagopalan K, Minkwitz M, et al, for the BOLDER Study Group. *Int Clin Psychopharmacol*. 2007;22:29-37. 6. Vieta E, Mullen J, Brecher M, et al. *Curr Med Res Opin*. 2005;21:923-934. 7. Sachs G, Chengappa KNR, Suppes T, et al. *Bipolar Disord*. 2004;6:213-223. 8. Data on file, AstraZeneca Pharmaceuticals LP, DA-SER-45.

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