

Reduced Hippocampus Volume Tied to Cannabis Use

BY MARY ANN MOON
Contributing Writer

Heavy cannabis users show marked reduction in hippocampus volume on high-resolution 3-T MRI imaging, investigators have reported. The volume reductions appear to correlate with the degree of exposure to the drug, according to Murat Yücel, Ph.D., of the University of Melbourne and associates. These findings “challenge the wide-

spread perception of cannabis as having limited or no neuroanatomical sequelae” and suggest that heavy use “may indeed be toxic to human brain tissue,” the investigators noted (Arch. Gen. Psychiatry 2008;65:694-701). Few brain imaging studies have been conducted in cannabis users, and the results have been inconsistent. “Indeed, despite strong evidence of neurotoxicity in the animal literature, to our knowledge no neuroimaging study has examined the

neurobiologic sequelae of long-term heavy cannabis use while controlling for the important confounds of polydrug abuse and co-occurring psychiatric disorders,” Dr. Yücel and his associates said. They used high-resolution 3-T MRI to assess volume in the hippocampus and the amygdala, two brain regions rich in cannabinoid receptors, in 15 men (mean age 40 years) who were regular heavy cannabis users and in 16 healthy nonusers matched for age, premorbid intelligence,

years of education, and anxiety symptoms. None of the subjects had any medical, neurologic, or psychiatric conditions, and none abused alcohol or other drugs. The mean duration of regular use was 19.7 years. The cannabis users showed a significant, 12% reduction in hippocampus volume and a smaller but still significant 7% reduction in amygdala volume, compared with the control subjects, said Dr. Yücel and his associates, who had no financial conflicts to disclose. The cannabis users also reported significantly greater symptoms on an assessment of subthreshold psychotic symptoms than did the controls, and they showed significantly poorer performance on a test of verbal learning ability. There also was a significant inverse association between cumulative cannabis exposure in the preceding 10 years and hippocampus volume in the left, but not the right, hemisphere. “Previous functional imaging studies have found reduced left hippocampal activation during cognitive performance in cannabis users, and there is evidence to suggest that hippocampal abnormalities in psychiatric disorders such as schizophrenia are more prominent in the left hemisphere,” they pointed out. All of which suggests “that the left hippocampus may be particularly vulnerable to the effects of cannabis exposure and may be more closely related to the emergence of psychotic symptoms,” Dr. Yücel and his associates said.

Naltrexone Tx Inhibits Pleasures From Drinking

TORONTO — Long-term treatment with extended-release naltrexone selectively inhibited the hedonic response associated with drinking alcohol while sparing the experience of pleasure associated with other activities such as reading and listening to music, a study has found. A total of 74 patients who participated in a 4-year trial comparing two doses of injectable extended-release naltrexone (Vivitrol) with placebo or a 3-year trial comparing the injectable drug with the oral formulation agreed to participate in an extension phase involving high- or low-dose naltrexone and a questionnaire, according to Dr. Charles O’Brien, Kenneth Appel Professor of Psychiatry, University of Pennsylvania, Philadelphia. The activities ranged from drinking alcohol to eating good food, and for each activity, respondents rated how pleasurable the activity was, Dr. O’Brien reported in a poster at the annual conference of the American Society of Addiction Medicine. Those who had consumed alcohol within the previous 90 days showed relatively low ratings of pleasure from drinking. Dr. O’Brien reported no financial conflicts of interest. —Nancy Walsh

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In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 8-weeks) of bipolar depression in 5% or more of patients treated with SEROQUEL (doses of 300 and 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.					
Table 4. Treatment-Emergent Adverse Experience Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression					
Body System/Preferred Term	SEROQUEL (n=698)	PLACEBO (n=347)	Body System/Preferred Term	SEROQUEL (n=698)	PLACEBO (n=347)
Gastrointestinal Disorders			Metabolism and Nutrition Disorders		
Dry Mouth	44%	13%	Increased Appetite	5%	3%
Constipation	10%	4%	Nervous System Disorders		
Dyspepsia	7%	4%	Sedation	30%	8%
Vomiting	5%	4%	Somnolence	28%	7%
General Disorders and Administrative Site Conditions			Dizziness	18%	7%
Fatigue	10%	8%	Lethargy	5%	2%
			Respiratory, Thoracic, and Mediastinal Disorders		
			Nasal Congestion	5%	3%

1 Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%). Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials:** Dose-related adverse events: Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response (p <0.05) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms: Dystonia Class Effect:** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

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Dose Groups	Placebo	75 mg	150 mg	300 mg	600 mg	750 mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	11%

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse events potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups. **Vital Signs and Laboratory Studies:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS). **Weight Gain:** In schizophrenia trials the proportions of patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania or nontherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight gain criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). In placebo controlled monotherapy clinical trials involving 3368 patients on SEROQUEL and 1515 on placebo, the incidence of at least one occurrence of neutrophil count $<1.0 \times 10^9/L$ among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with SEROQUEL, compared to 0.1% (2/1349) in patients treated with placebo. (See PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis.) In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed. **Hyperglycemia:** In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dL) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.8% of patients). In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with SEROQUEL and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥ 126 mg/dL or a non fasting blood glucose ≥ 200 mg/dL was 3.5% for quetiapine and 2.1% for placebo. In a 24 week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycaemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥ 200 mg/dL was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥ 126 mg/dL was 2.6%. **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/169) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to >120 beats per minute. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see PRECAUTIONS). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported events are included except those already listed in Table 2 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System:** Frequent: hypertonia, dysarthria; Infrequent: abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, nystagmus; Rare: apathia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma. **Body as a Whole:** Frequent: flu syndrome; Infrequent: neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; Rare: abdomen enlarged. **Digestive System:** Frequent: anorexia; Infrequent: increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence,

*adjusted for gender

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gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema. Rare: glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. Cardiovascular System: Frequent: palpitation; Infrequent: vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; Rare: angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. Respiratory System: Frequent: pharyngitis, rhinitis, cough increased, dyspnea; Infrequent: pneumonia, epistaxis, asthma; Rare: hiccups, hyperventilation. Metabolic and Nutritional System: Frequent: peripheral edema; Infrequent: weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; Rare: glycosuria, gout, hand edema, hypokalemia, diuretic intoxication. Skin and Appendages System: Frequent: sweating; Infrequent: pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; Rare: exfoliative dermatitis, psoriasis, skin discoloration. Urogenital System: Infrequent: dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis*, orchitis*; Rare: gynecastasia*, nocturia, polyuria, acute kidney failure. Special Senses: Infrequent: conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; Rare: abnormality of accommodation, deafness, glaucoma. Musculoskeletal System: Infrequent: pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. Hemic and Lymphatic System: Frequent: leukopenia; Infrequent: leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia, lymphadenopathy, cyanosis; Rare: hemolysis, thrombocytopenia. Endocrine System: Infrequent: hypothyroidism, diabetes mellitus; Rare: hyperthyroidism. Post Marketing Experience: Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: anaphylactic reaction, and restless legs. Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy, hyponatremia, myocarditis, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Stevens-Johnson Syndrome (SJS).					

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: SEROQUEL is not a controlled substance. **Physical and Psychologic Dependence:** SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE Human experience: In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see PRECAUTIONS: Orthostatic Hypotension). One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation. **Management of Overdosage:** In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSEAGE AND ADMINISTRATION: **Bipolar Disorder:** Depression *Usual Dose:* SEROQUEL should be administered once daily at bedtime to reach 300 mg/day by day 4.

Recommended Dosing Schedule					
Day	Day 1	Day 2	Day 3	Day 4	
SEROQUEL	50 mg	100 mg	200 mg	300 mg	

In the clinical trials supporting effectiveness, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for days 1-4 respectively. Patients receiving 600 mg increased to 400 mg on day 5 and 600 mg on day 8 (Week 1). Antidepressant efficacy was demonstrated with SEROQUEL at both 300 mg and 600 mg however, no additional benefit was seen in the 600 mg group. **Mania Usual Dose:** When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in bid doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in bid divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicates that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials. **Schizophrenia Usual Dose:** SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg/day by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective. Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials. **Dosing in Special Populations:** Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see CLINICAL PHARMACOLOGY in full Prescribing Information). When indicated, dose escalation should be performed with caution in these patients. Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient. The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under PRECAUTIONS). **Maintenance Treatment:** While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment. **Reinitiation of Treatment in Patients Previously Discontinued:** Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed. **Switching from Antipsychotics:** There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

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