

# Visual Processing Abnormal in Schizophrenia

VITALS

**Major Finding:** Electroencephalographic monitoring found the P1 component reduced in individuals at risk for psychosis. The deficits were related to worse performance on working memory in a task with short stimulus presentation times, though high schizotypes were no different from controls in central executive and memory tasks that allowed longer stimulus duration.

**Data Source:** Prospective study conducted at the University of Manchester with volunteers.

**Disclosures:** The authors reported no potential conflicts of interest.

BY CAROLINE HELWICK

FROM THE ANNUAL CONGRESS OF THE EUROPEAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AMSTERDAM – Visual processing abnormalities can be observed not only in schizophrenia but in persons at risk for psychosis, according to a study by investigators in the United Kingdom presented at the congress. “We wanted to clarify the importance of early visual deficits for the formation of cognitive deficits in the schizophrenia spectrum,”

said Ivan Koychev, a doctoral candidate at the University of Manchester, Neuroscience and Psychiatry Unit.

“Our study confirmed that visual deficits are not due to the overt clinical phenotype, but are rather characteristic of the schizophrenia spectrum.”

Mr. Koychev and his colleagues carried out an event-related potential (ERP) study using a working memory task on volunteers exhibiting high and low levels of schizophrenia-like personality traits. The hypothesis was that the high schizotypes would have early visual deficits (P1 component reduction) and working memory similar to that observed in persons with schizophrenia and their first-degree relatives. They also hypothesized that the working memory deficits would be more pronounced on tasks that allow only short stimulus presentation, but would be more difficult to demonstrate in tasks that allow ample time for stimulus processing.

Participants completed a visual delayed discrimination task where they were shown stimuli briefly (400 ms),



**‘Our study confirmed that visual deficits ... are rather characteristic of the schizophrenia spectrum.’**

MR. KOYCHEV

which they compared to target cues presented after a 6-second delay.

Researchers also recorded their performance on several tests of cognition.

The high schizotypal and low schizotypal (control) subjects did not differ in their reaction times to the task, which increased significantly with the working memory load ( $P$  less than .001). However, the performance on the task was significantly worse in the high schizotypes, as they identified correctly a lower number of target cues ( $P = .034$ ), Mr. Koychev said.

“There was no difference in reaction times but their behavior was different in that the high schizotypes were recognizing fewer objects. We then asked if this was reflected in visual deficits, and we found reduced potential in the high schizotypes. This was true for encoding and retrieval. When subjects were shown images, the visual cortex did not respond as robustly,” he said in an interview.

The P1 ERP component was significantly reduced in the high schizotypes’ sample, both in the encoding ( $P = .034$ ; effect size, .0351) and retrieval ( $P = .029$ ; effect size .353) phases of the task. None of the later components (N1, P2) was significantly different between the groups. The P1 abnormality in the schizotypal subjects was reflected by abnormalities in the alpha evoked oscillations (Neuropsychologia 2010;48:2205-17).

“Our study confirmed the hypothesis that the P1 component is reduced in individuals at risk of psychosis,” Dr. Koychev said. ■

## Silenor<sup>®</sup> (doxepin) tablets for oral administration

Brief summary of Prescribing Information. For currently Prescribing Information, consult official package insert.

### INDICATIONS AND USAGE

Silenor is indicated for the treatment of insomnia characterized by difficulty with sleep maintenance. The clinical trials performed in support of efficacy were up to 3 months in duration.

### CONTRAINDICATIONS

#### Hypersensitivity:

Silenor is contraindicated in individuals who have shown hypersensitivity to doxepin HCl, any of its inactive ingredients, or other dibenzoxepines.

#### Co-administration With Monoamine Oxidase Inhibitors (MAOIs):

Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Do not administer Silenor if patient is currently on MAOIs or has used MAOIs within the past two weeks. The exact length of time may vary depending on the particular MAOI dosage and duration of treatment.

#### Glaucoma and Urinary Retention:

Silenor is contraindicated in individuals with untreated narrow angle glaucoma or severe urinary retention.

### WARNINGS AND PRECAUTIONS

#### Need to Evaluate for Comorbid Diagnoses:

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Exacerbation of insomnia or the emergence of new cognitive or behavioral abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with hypnotic drugs.

#### Abnormal Thinking and Behavioral Changes:

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a hypnotic, with amnesia for the event) have been reported with hypnotics. These events can occur in hypnotic-naïve as well as in hypnotic-experienced persons. Although behaviors such as “sleep-driving” may occur with hypnotics alone at therapeutic doses, the use of alcohol and other CNS depressants with hypnotics appears to increase the risk of such behaviors, as does the use of hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Silenor should be strongly considered for patients who report a “sleep-driving” episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a hypnotic. As with “sleep-driving”, patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably.

#### Suicide Risk and Worsening of Depression:

In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), has been reported in association with the use of hypnotics. Doxepin, the active ingredient in Silenor, is an antidepressant at doses 10- to 100-fold higher than in Silenor. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Risk from the lower dose of doxepin in Silenor cannot be excluded. It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

#### CNS Depressant Effects:

After taking Silenor, patients should confine their activities to those necessary to prepare for bed. Patients should avoid engaging in hazardous activities, such as operating a motor vehicle or heavy machinery, at night after taking Silenor, and should be cautioned about potential impairment in the performance of such activities that may occur the day following ingestion. When taken with Silenor, the sedative effects of alcoholic beverages, sedating antihistamines, and other CNS depressants may be potentiated. Patients should not consume alcohol with Silenor. Patients should be cautioned about potential additive effects of Silenor used in combination with CNS depressants or sedating antihistamines.

#### ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of labeling:

- Abnormal thinking and behavioral changes.
- Suicide risk and worsening of depression.
- CNS Depressant effects.

#### Clinical Trials Experience:

The pre-marketing development program for Silenor included doxepin HCl exposures in 1017 subjects (580 insomnia patients and 437 healthy subjects) from 12 studies conducted in the United States. 863 of these subjects (580 insomnia patients

and 283 healthy subjects) participated in six randomized, placebo-controlled efficacy studies with Silenor doses of 1mg, 3 mg, and 6 mg for up to 3-months in duration. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. However, data from the Silenor studies provide the physician with a basis for estimating the relative contributions of drug and non-drug factors to adverse reaction incidence rates in the populations studied.

#### Associated with Discontinuation of Treatment:

The percentage of subjects discontinuing Phase 1, 2, and 3 trials for an adverse reaction was 0.6% in the placebo group compared to 0.4%, 1.0%, and 0.7% in the Silenor 1 mg, 3 mg, and 6 mg groups, respectively. No reaction that resulted in discontinuation occurred at a rate greater than 0.5%.

#### Adverse Reactions Observed at an Incidence of $\geq 2\%$ in Controlled Trials:

Table 1 shows the incidence of treatment-emergent adverse reactions from three long-term (29 to 85 days) placebo-controlled studies of Silenor in adult (N=221) and elderly (N=494) subjects with chronic insomnia. Reactions reported by investigators were classified using a modified MedDRA dictionary of preferred terms for the purposes of establishing incidence. The table includes only reactions that occurred in 2% or more of subjects who received Silenor 3 mg or 6 mg in which the incidence in subjects treated with Silenor was greater than the incidence in placebo-treated subjects.

#### Incidence (%) of Treatment-Emergent Adverse Reactions in Long-term Placebo-Controlled Clinical Trials

System Organ Class Preferred Term*	Placebo (N=278)	Silenor 3 mg (N=157)	Silenor 6 mg (N=203)
Nervous System Disorders			
Somnolence/Sedation	4	6	9
Infections and Infestations			
Upper Respiratory Tract Infection/Nasopharyngitis	2	4	2
Gastroenteritis	0	2	0
Gastrointestinal Disorders			
Nausea	1	2	2
Vascular Disorders			
Hypertension	0	3	<1

\*Includes reactions that occurred at a rate of  $\geq 2\%$  in any Silenor-treated group and at a higher rate than placebo.

The most common treatment-emergent adverse reaction in the placebo and each of the Silenor dose groups was somnolence/sedation.

#### Studies Pertinent to Safety Concerns for Sleep-promoting Drugs:

##### Residual Pharmacological Effect in Insomnia Trials:

Five randomized, placebo-controlled studies in adults and the elderly assessed next-day psychomotor function within 1 hour of awakening utilizing the digit-symbol substitution test (DSST), symbol copying test (SCT), and visual analog scale (VAS) for sleepiness, following night time administration of Silenor. In a one-night, double-blind study conducted in 565 healthy adult subjects experiencing transient insomnia, Silenor 6 mg showed modest negative changes in SCT and VAS. In a 35-day, double-blind, placebo-controlled, parallel group study of Silenor 3 and 6 mg in 221 adults with chronic insomnia, small decreases in the DSST and SCT occurred in the 6 mg group. In a 3-month, double-blind, placebo-controlled, parallel group study in 240 elderly subjects with chronic insomnia, Silenor 1 mg and 3 mg was comparable to placebo on DSST, SCT, and VAS.

#### DRUG INTERACTIONS

##### Cytochrome P450 Isozymes:

Silenor is primarily metabolized by hepatic cytochrome P450 isozymes CYP2C19 and CYP2D6, and to a lesser extent, by CYP1A2 and CYP2C9. Inhibitors of these isozymes may increase the exposure of doxepin. Silenor is not an inhibitor of any CYP isozymes at therapeutically relevant concentrations. The ability of Silenor to induce CYP isozymes is not known.

##### Cimetidine:

Silenor exposure is doubled with concomitant administration of cimetidine, a nonspecific inhibitor of CYP isozymes. A maximum dose of 3 mg is recommended in adults and elderly when cimetidine is co-administered with Silenor.

##### Alcohol:

When taken with Silenor, the sedative effects of alcohol may be potentiated.

##### CNS Depressants and Sedating Antihistamines:

When taken with Silenor, the sedative effects of sedating antihistamines and CNS depressants may be potentiated.

##### Tolazamide:

A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 g/day) 11 days after the addition of oral doxepin (75 mg/day).

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy:

###### Pregnancy Category C:

There are no adequate and well-controlled studies of Silenor in pregnant women. Silenor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Administration of doxepin to pregnant animals resulted in adverse effects on offspring development at doses greater than the maximum recommended human dose (MRHD) of 6 mg/day. When doxepin (30, 100, and 150 mg/kg/day) was administered orally to pregnant rats during the period of organogenesis, developmental toxicity (increased incidences of fetal structural abnormalities and decreased fetal body weights) was noted at  $\geq 100$  mg/kg/day. The plasma exposures (AUC) at the no-effect dose for embryo-fetal developmental toxicity in rats (30 mg/kg/day) are approximately 6 and 3 times the plasma AUCs for doxepin and nordoxepin (the primary metabolite in humans), respectively, at the MRHD. When administered orally to pregnant rabbits (10, 30, and 60 mg/kg/day) during the period of organogenesis, fetal body weights were reduced at the highest dose in the absence of maternal toxicity. The plasma exposures (AUC) at the no-effect dose for developmental effects (30 mg/kg/day) are approximately 6 and 18 times the plasma AUCs for doxepin and nordoxepin, respectively, at the MRHD. Oral administration of doxepin (10, 30, and 100 mg/kg/day) to rats throughout the pregnancy and lactation periods resulted in decreased pup survival and transient growth delay at the highest dose. The plasma exposures (AUC) at the no-effect dose for adverse effects on pre- and postnatal development in rats (30 mg/kg/day) are approximately 3 and 2 times the plasma AUCs for doxepin and nordoxepin, respectively, at the MRHD.

##### Labor and Delivery:

The effects of Silenor on labor and delivery in pregnant women are unknown.

##### Nursing Mothers:

Doxepin is excreted in human milk after oral administration. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking the higher dose of doxepin used to treat depression. Caution should be exercised when Silenor is administered to nursing women.

##### Pediatric Use:

The safety and effectiveness of Silenor in pediatric patients have not been evaluated.

##### Geriatric Use:

A total of 362 subjects who were  $\geq 65$  years and 86 subjects who were  $\geq 75$  years received Silenor in controlled clinical studies. No overall differences in safety or effectiveness were observed between these subjects and younger adult subjects. Greater sensitivity of some older individuals cannot be ruled out. Sleep-promoting drugs may cause confusion and over-sedation in the elderly. A starting dose of 3 mg is recommended in this population and evaluation prior to considering dose escalation is recommended.

##### Use in Patients With Hepatic Impairment:

Patients with hepatic impairment may display higher doxepin concentrations than healthy individuals. Initiate Silenor treatment with 3 mg in patients with hepatic impairment and monitor closely for adverse daytime effects.

##### Use in Patients With Sleep Apnea:

Silenor has not been studied in patients with obstructive sleep apnea. Since hypnotics have the capacity to depress respiratory drive, precautions should be taken if Silenor is prescribed to patients with compromised respiratory function. In patients with severe sleep apnea, Silenor is ordinarily not recommended for use.

#### OVERDOSAGE

Doxepin is routinely administered for indications other than insomnia at doses 10- to 50-fold higher than the highest recommended dose of Silenor.

The signs and symptoms associated with doxepin use at doses several-fold higher than the maximum recommended dose (Excessive dose) of Silenor for the treatment of insomnia are described, as are signs and symptoms associated with higher multiples of the maximum recommended dose in the full prescribing information.

#### PATIENT COUNSELING INFORMATION

Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with hypnotics, should counsel them in appropriate use, and should instruct them to read the Medication Guide.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.

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