

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA® (n = 1796), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment [see *Clinical Pharmacology* (12.3) in full PI], who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Dosage and Administration* (2.5) in full PI].

Renal Impairment: Dosing must be individualized according to the patient's renal function status [see *Dosage and Administration* (2.5) in full PI].

Hepatic Impairment: No dosage adjustment is required in patients with mild to moderate hepatic impairment. INVEGA® has not been studied in patients with severe hepatic impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: INVEGA® (paliperidone) is not a controlled substance.

Abuse: Paliperidone has not been systematically studied in animals or humans for its potential for abuse. It is not possible to predict 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 INVEGA® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Dependence: Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

OVERDOSAGE

Human Experience: While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA® was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdosage: There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, 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, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for 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 an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

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 paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

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Manufactured for:

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Evidence vs experience

Concerning the role of "evidence" in psychiatric practice ("Are psychiatrists more evidence-based than psychologists?" From the Editor, CURRENT PSYCHIATRY, December 2009, p. 16-18), my question is whether psychiatrists who consider themselves evidence-based achieve better clinical results than those who do not. I suspect there is no significant difference. Of course, this question will never be answered to Dr. Nasrallah's standards. No pharmaceutical or insurance companies are interested enough because, with the mediation of psychiatric thought leaders, they have succeeded in redefining the nature of and criteria for evidence. They now own it. To what degree it strongly pertains to the real world is an open question.

As a psychiatrist with several decades of experience who works on the front lines, I am leery of the growing biomedical depersonalization and algorithmic regimentation of treatment. I am less optimistic about the kind of progress implied in Dr. Nasrallah's editorial. I do not believe it is his place to tell colleagues how they should practice. Psychiatric treatment mostly occurs in the context of a one-to-one relationship, and evidence generated by the research industry must be scrutinized according to the individual patient's exigencies and factors affecting the patient's life and clinical condition. This is a process of clinical judgment, which integrates not only the narrowly defined, research-based evidence Dr. Nasrallah mentioned but also a psychiatrist's experience, which there appears to be little place for in psychiatry's brave new world. It may be that psychologists maintain a certain clinical advantage over psychiatrists in this regard.

Edmond Zeldin, MD
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Dr. Nasrallah responds

I welcome Dr. Zeldin's critical remarks. As a clinician, I too value my more than 3 decades of clinical experience, but as a researcher I also recognize that it is insufficient to provide optimal care. On the first page of Dr. Gregory Gray's book Evidence-based psychiatry,¹ the first heading states "Clinical practice is not always evidence-based." Dr.

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Gray says that evidence-based medicine (EBM) is "the application of a knowledge of medical informatics and clinical epidemiology to the treatment of individual patients and involves the integration of the best research evidence with clinical expertise and patient values."

The EBM concept was initiated by D.L. Sackett et al in 1996,² not by pharmaceutical companies. However, all drug companies must conduct strictly evidence-based clinical trials (double-blind, placebo-controlled, and sufficiently powered sample size) on experimental drugs before these agents can be approved by the FDA. The large FDA studies conducted by industry are part of EBM that are adopted in clinical practice. However, some non-FDA drug

company studies are self-serving and not evidence-based.³

I recently reviewed 237 meta-analytic studies in schizophrenia,⁴ and only 30 of those studies address pharmacology. Other meta-analyses included: genetics (58 studies), cognition (38), neuroimaging (23), psychopathology (22), psychosocial therapies (19), neurophysiology (13), epidemiology (12), neurochemistry (8), development (7), and post-mortem (3). Those meta-analytic studies sift through thousands of published papers and help provide part of the "evidence" in schizophrenia. Similar meta-analyses are conducted for all psychiatric disorders.

Finally, I did not instruct readers that they must practice in an evidence-based manner. However, I implied that

many patients are not receiving effective evidence-based care in both psychotherapy (by psychologists) and psychopharmacology (by psychiatrists). Many clinicians practice "experience-based medicine" or "eminence-based medicine," but I believe EBM should be the basic framework into which we integrate our clinical experience or expert opinions to provide optimal care for our patients.

Henry A. Nasrallah, MD
Editor-in-Chief

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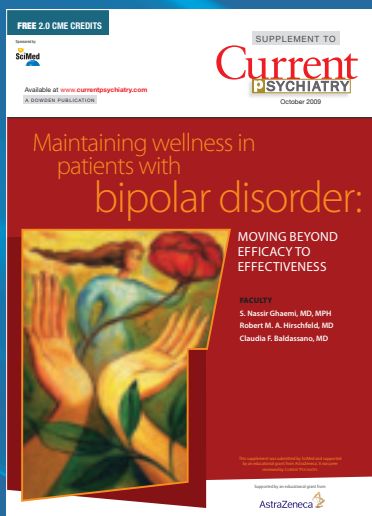
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