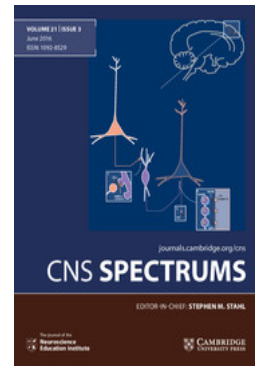

Schizophrenia Risk and Paternal Age: A Potential Role for De Novo Mutations in Schizophrenia Vulnerability Genes

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Schizophrenia Risk and Paternal Age: A Potential Role for De Novo Mutations in Schizophrenia Vulnerability Genes

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ABSTRACT

How schizophrenia (SZ) is maintained at roughly 1% of the population despite diminished reproduction is one puzzle currently facing researchers. De novo mutations were first proposed over half a century ago as a source for new SZ genes. Current evidence linking advancing paternal age to SZ risk makes revisiting this hypothesis important. Advancing paternal age is the major source of new mutations in the human population. This article will examine potential mechanisms whereby parental age may impact new mutations, as well as review recent data supporting such a hypothesis.

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INTRODUCTION

Although the hereditary nature of schizophrenia (SZ) is beyond dispute, no particular gene has been shown to significantly account for SZ in the population. SZ segregation patterns within families have not revealed a dominant, recessive, or sex-linked mode of inheritance. This would be consistent with a single-gene effect. Rather, SZ is a more complex disorder. Such conditions are likely to be etiologically heterogeneous. Their genetic components may derive from the interaction of a number of genes (epistasis) or from genes with incomplete penetrance or variable expressivity, wherein additional environmental factors may be necessary for the final expression of the disease. Because a number of such genes could be carried but not expressed as SZ, healthy parents can transmit SZ vulnerability genes to their offspring. Thus, an affected individual with no family history of SZ can still have a genetic disease. Nevertheless, individuals with otherwise unaffected family members are often considered to have an environmentally caused form of SZ. A large body of research has been directed toward identifying in utero events, birth traumas, and other exposures that might be nongenetic routes to SZ. Whether the SZ cases without any family history—the so-called sporadic cases—have a lesser genetic load and a greater exposure to environmental factors remains enigmatic.

MUTATIONS

Another possibility, rarely explored until recently, is that new mutations are constantly arising in SZ genes. Although this idea was proposed 50 years ago, the required mutation rates were considered to be too high to account for the prevalence of SZ. The hypothesis was discarded.[1-3] However, recent data show that humans may acquire 100 mutations per individual per generation, including several deleterious mutations, one or two of which may be passed on to later generations.[4] New mutations might explain how SZ genes are maintained in the population even though those with the disease are far less likely to bear children than are unaffected individuals. It could also account for some of the inconsistencies in segregation and linkage studies in SZ families. New mutations could also explain the greater recurrence risk for SZ in the children of SZ probands (~10%) than in their parents (~5%)[5] if the gene mutations arising spontaneously in the paternal germ line were subsequently inherited by later generations.

In 1912, Weinberg[6] had observed that achondroplastic dwarfism was more common in last-born siblings and suggested that aging maternal and paternal germ cells may be prone to mutation. Subsequently, Penrose[7] demonstrated that later paternal age, but not maternal age, was predictive of de novo mutations. He proposed that mutations arose by deoxyribonucleic acid (DNA) copy errors that accumulate over many replication cycles that occur in the male germ line. Since approximately 500 million spermatozoa are released in each ejaculation, spermatogenesis continually occurs. The spermatogonial cells replicate every 16 days, approximating 200 divisions by age 20 years and 660 divisions by age 40 years,[8] therefore yielding many opportunities for mutations (Figure 1). By contrast, oocytes undergo only 24 cell divisions, of which all but the last occur before a woman's birth.

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Now, it is accepted that the major source of new mutations in human populations is advancing paternal age.[9] The mutations that arise in the male germ line are amplified in clones of spermatozoa over the repeated cell divisions that occur with paternal aging, including DNA repair enzyme insufficiency, free radicals, oxidative damage, radiation, nutritional deficiency, chemotherapy, and high temperatures, the factors that cause mutations in spermatozoa (the same factors that induce mutations in somatic cells).[10-12] Cigarette smoking has also been linked to genetic damage in spermatozoa, and free radical-induced mutations are theorized to be a common cause of male infertility. Both of these exposures have been implicated in the etiology of childhood cancer.[13,14] Furthermore, as men age, mutations may increase because spermatogenesis occurs in the presence of declining testosterone, lower levels of DNA proofreading and repair enzymes, and reduced antioxidant enzyme activity, along with the vascular limitations and reduced cellular efficiency that accompany aging in other tissues.[15] The amount of new mutations tolerated by an organism is a trade-off between the cellular energy expenditures via DNA proofreading and repair and the loss of offspring viability from mutations. Since most mutations decrease fitness, evolution will sustain genomes with efficient DNA repair enzymes. However, there would not have been much evolutionary pressure to maintain high DNA replication accuracy in older men, given the lesser longevity of man over much of evolutionary time.

It has been known for quite some time that mutations related to advancing paternal age cause several autosomal dominant diseases when these occur as sporadic (nonfamilial) cases, including achondroplasia, Apert's syndrome, and progeria.[16-18] But recent studies have shown that a number of common complex genetic disorders are also related to advancing paternal age, including prostate cancer,[19] nervous system cancer,[20] and certain birth defects (Table 1).[21]

PATERNAL AGE AND SCHIZOPHRENIA

If SZ were related to new mutations, then we would expect it to be related to paternal age. In a recent study,[22] the association of SZ and parental age in an 89,722-member population birth cohort were examined. Of the 1,337 offspring admitted to psychiatric units prior to 1998, 658 were diagnosed with SZ and related nonaffective psychoses (*International Classification of Diseases*, Ninth Revision, diagnosis [F20–F29]). Proportional hazards and regression analysis (controlled for maternal age, gender, ethnicity, socioeconomic status, and duration of marriage) revealed that the age of the father was indeed a strong and significant predictor of SZ diagnoses in the offspring. Compared with offspring of fathers <25 years of age, the relative risk of SZ increased monotonically in each 5-year age group, reaching 2.02 (95% CI: 1.17-3.51) in men 45–49 years of age and 2.96 (95% CI: 1.60-5.47) in offspring of fathers >50 years of age. There was no linearly increasing risk for mothers' age (Figure 2). By contrast, there was no similar significant relationship of fathers' age and illness risk in the group of patients who did not have SZ.

A similar association of increasing SZ risk with advancing paternal age was subsequently replicated in a birth cohort from California by Brown and colleagues[23] and in several other birth cohorts in the Aarhus, Brisbane, Dublin, Malmo Consortium.[24]

It can be argued that the relationship between paternal age and SZ risk is an artifact of delayed parental childbearing, perhaps because of social inadequacies in psychiatrically vulnerable parents. However, if parental psychiatric vulnerability delays childbearing, then paternal age should be older in familial SZ cases than in sporadic cases. This possibility was exam-

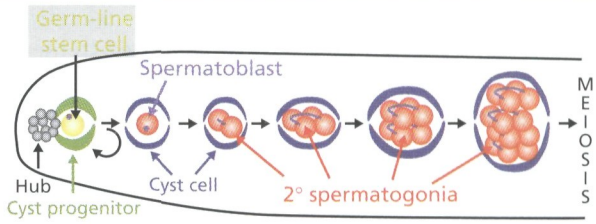

FIGURE 1. The testes contain an arrangement of the spermatogonia and their progeny within seminiferous tubules. The large germ-line stem cells are anchored around a "hub" of about a dozen nondividing somatic cells. Two elongated somatic cells are nestled around each germ-line stem cell, which are stem cells for the somatic cyst lineage (cyst progenitor cells). Spermatogenesis begins as a germ-line stem cell divides asymmetrically, generating one daughter that retains stem cell fate and remains adjacent to the hub, and a second daughter cell that becomes a spermatoblast. The spermatoblast differentiates after it has undergone an amplification, clonally expanding the population of now-secondary spermatogonia. The mitoses occur with incomplete separation of the cytoplasm, such that all germ-cell daughters are interconnected by persistent cytoplasmic bridges. Snaking through each interconnected cell is a cytoskeletal and membranous structure known as a fusome. The resulting clone of 16 germ cells exits the mitotic cycle and enters the meiotic phase of growth, and the cells are now called spermatocytes.

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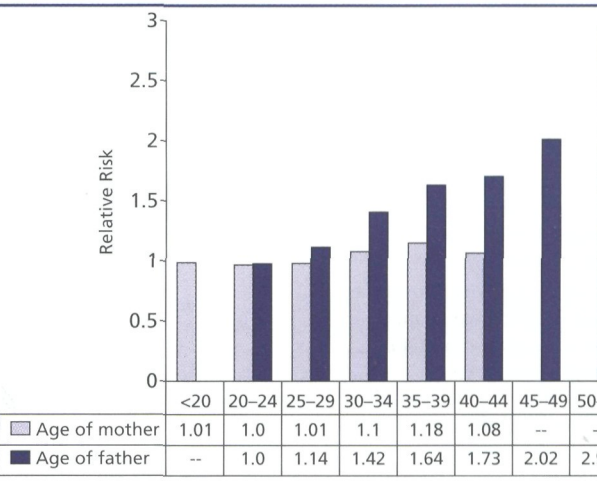

	<20	20–24	25–29	30–34	35–39	40–44	45–49	50–54
Age of mother	1.01	1.0	1.01	1.1	1.18	1.08	--	--
Age of father	--	1.0	1.14	1.42	1.64	1.73	2.02	2.96

FIGURE 2. An estimated relationship between paternal age and schizophrenia risk.

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ined in a series of SZ research patients[25] which showed, to the contrary, that paternal age was significantly older for the sporadic cases. Taken together, these findings are consistent with a significant role for new mutations in SZ vulnerability.

If mutations explain the paternal age effect, there are several ways that they might relate to SZ. The type of new mutation that arises most frequently in the paternal gametes is a single base-pair change. Thus, a mutation which enhances SZ risk could possibly occur in a specific SZ gene. This is the case in achondroplastic dwarfism, where over 90% of the cases are sporadic, and in over 97% of such persons the de novo mutation occurs at a "hot spot" in a single codon leading to a missense mutation in the fibroblast growth factor 3 gene.[26,27] Such de novo mutations for SZ need to occur in a dominant or partially dominant gene if inheritance of a single mutated allele confers an increased risk for the disease. However, given that thousands of genes play a role in neurodevelopment, it is possible that mutations in many genes could cause SZ as a final common phenotype.

Increased SZ risk could also be a consequence of progressive DNA trinucleotide expansions in one or several genes that participate in neurodevelopment. This effect could be more marked as paternal age advances and the number of cell division cycles increase in the male germ line, since the possibility of further trinucleotide expansion occurs at each DNA replication. Repeat expansions have been demonstrated in a number of neuropsychiatric disorders, including myotonic dystrophy, fragile X syndrome, spinocerebellar ataxias,[28] and Huntington's disease.[29] The gender of the transmitting parent is frequently a major factor influencing anticipation,[30] with many disorders showing greater trinucleotide repeat expansion with paternal over maternal inheritance.[31] For example, in early-onset Huntington's disease the offspring had a younger age of onset than their fathers.[32] For SZ, too, the onset appears to be earlier in successive generations of multiply affected pedigrees, consistent with anticipation.[33,34] Finally, anticipation has reported to be stronger for paternal than for maternal transmission of SZ in some but not all studies.[35-38]

Such parent-of-origin effects are also consistent with genetic imprinting. Imprinting is a form of gene regulation in which gene expression depends on whether the allele was inherited from the male or female parent in the prior generation. Imprinted genes that are only expressed if paternally inherited are reciprocally silenced at the maternal allele, and the contrary is true for maternally expressed genes. Genes are silenced by DNA methylation, which may preclude transcription factor binding, and by alterations in chromatin structure. The inherited methylation pattern is maintained in somatic cell divisions but is erased in the primordial germ cells and reestablished late in gametogenesis. The monoallelic pattern of gene expression is maintained in offspring of the same sex and is reversed when genes are transmitted through individuals of the opposite gender. Imprinted genes do not conform to Mendelian principles since only one allele from the prior generation is expressed, even though an equivalent amount of genetic material (other than sex chromosomes) is inherited from both parents. Hundreds of human genes are likely to be genetically imprinted.

Paternal age may have a detrimental effect on genetic imprinting because paternal genes are imprinted during spermatogenesis. Environmental exposures, in addition to genetic mechanisms, can cause epigenetic changes in imprinted genes,[39] and spermatozoan DNA may be especially susceptible to noxious exposures because of the ongoing replication during spermatogenesis and the unstable nature of genetic imprinting. Many of the mutations associated with advancing paternal age are at the sites where methylation of the imprinted genes occur.[40] This is consistent with imprinted gene involvement. It may be relevant that SZ has shown genetic linkage to chromosome 15q13–q14,[41] a region near many imprinted genes, including those for Angelman and Prader–Willi syndromes.[42] Moreover, Prader-Willi syndrome, in which the paternally imprinted gene is deleted, frequently includes the presence of a SZ-like psychosis.[43]

Given the enormous effort that has been brought to bear on deciphering the origins of SZ vulnerability, it may seem surprising that these data on paternal age and SZ are only now being described. However, older paternal age in probands with SZ has been previously reported by a number of authors.

TABLE. SOME GENETIC CONDITIONS ASSOCIATED WITH ADVANCED PATERNAL AGE

Autosomal Disorders	X-linked Disorders	Complex Disorders
Achondroplasia	Hemophilia A	Schizophrenia
Neurofibromatosis	Hemophilia B	Costello's syndrome
Marfan's syndrome	Retinitis pigmentosa	Congenital heart defect
Treacher Collin's syndrome	Hunter's syndrome	Hydrocephaly
Waardenburg syndrome	Duchenne's muscular dystrophy	Neural tube defect
Osteogenesis imperfecta	Fragile X syndrome	Mental retardation
Apert's syndrome	Lesch-Nyan's syndrome	Dystonic cerebral palsy
MEN II	Incontinentia pigmenti	Prostrate cancer
Cruzen's syndrome		Retinoblastoma
Pfeiffer's syndrome		Wilms tumor
Progeria		Renal agenesis idiopathic torsion dystonia
Bruton's ammaglobulinemia		

MEN II=multiple endocrine neoplasia, type II.

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There were several reports in the 1950s and 1960s of later paternal age in SZ patients.[44-46] More recently, Hare and Moran[47] came up with the same findings while comparing a large series of cases with a representative sample of the population, as did another study that used the same control group.[48] Earlier data showing later paternal age in SZ received little attention. This association was not considered to reflect a role for de novo mutations for individuals with sporadic SZ, although similar findings in other medical conditions implicated a role for de novo mutations in disease etiology. It is unclear why these results in SZ were considered to be artifacts of methodologic limitations or, if valid, as resulting from delayed marriage and childbearing by psychiatrically vulnerable parents or other confounds. The reason may lie in our past view of SZ as a functional disease related to faulty parenting or weak ego boundaries rather than as a medical condition with biological underpinnings.

CONCLUSION

This review has considered some recent data supporting an association between SZ risk in offspring and the age of the father. As described, new mutations are related to advancing paternal age because point mutations, which occur over the many cell replication cycles in spermatogenesis, can accumulate in clones of spermatogonia as men age. This mechanism may contribute a significant proportion of SZ risk, depending on the father's age in the population. SZ may thus be one of a number of neurodevelopmental disorders that have been related to advanced paternal age. The risk of SZ with advancing paternal age may have implications for public health. A reduction in the mean paternal age would lead to the primary prevention of a portion of this devastating illness. CNS

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***Weight Loss:* In the controlled trials, approximately 26% of women on high doses of Exelon (greater than 9 mg/day) had weight loss of equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.**

Anorexia: In the controlled clinical trials, of the patients treated with an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course or the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia: Exelon as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions: Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6-12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary: Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions: Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions: Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS: Information for Patients and Caregivers: Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Drug-Drug Interactions: *Effect of Exelon® (rivastigmine tartrate) on the Metabolism of Other Drugs:* Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m² basis.

Rivastigmine was clastogenic in two *in vitro* assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three *in vitro* assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the *in vivo* mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m² basis.

Pregnancy: *Pregnancy Category B:* Reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 2.3 mg-base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m² basis) revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m² basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Exelon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether rivastigmine is excreted in human breast milk. Exelon has no indication for use in nursing mothers.

Pediatric Use: There are no adequate and well-controlled trials documenting the safety and efficacy of Exelon in any illness occurring in children.

ADVERSE REACTIONS: Adverse Events Leading to Discontinuation: The rate of discontinuation due to adverse events in controlled clinical trials of Exelon® (rivastigmine tartrate) was 15% for patients receiving 6-12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on Exelon compared to 4% for those on placebo.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)	Placebo (n=788)	Exelon ≥6-12 mg/day (n=987)	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)
Event / % Discontinuing						
Nausea	<1	8	<1	1	1	8
Vomiting	<1	4	<1	1	<1	5
Anorexia	0	2	<1	1	<1	3
Dizziness	<1	2	<1	1	<1	2

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon: The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions: Exelon use is associated with significant nausea, vomiting, and weight loss *(see WARNINGS)*.

Adverse Events Reported in Controlled Trials: Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 6-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined on the incidence of adverse events in the controlled studies. Nausea, vomiting and weight loss were more frequent in women than men.

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Exelon® (6-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Exelon (6-12 mg/day) (n=1189)
Percent of Patients with any Adverse Event	79	92
Autonomic Nervous System		
Sweating increased	1	4
Syncope	2	3
Body as a Whole		
Accidental Trauma	9	10
Fatigue	5	9
Asthenia	2	6
Malaise	2	5
Influenza-like Symptoms	2	3
Weight Decrease	<1	3
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	21
Headache	12	17
Somnolence	3	5
Tremor	1	4
Gastrointestinal System		
Nausea	12	47
Vomiting	6	31
Diarrhea	11	19
Anorexia	3	17
Abdominal Pain	6	13
Dyspepsia	4	9
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	9
Confusion	7	8
Depression	4	6
Anxiety	3	5
Hallucination	3	4
Aggressive Reaction	2	3
Resistance Mechanism Disorders		
Urinary Tract Infection	6	7
Respiratory System		
Rhinitis	3	4

Other adverse events observed at a rate of 2% or more on Exelon 6-12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infections, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Other Adverse Events Observed During Clinical Trials: Exelon has been administered to over 5297 individuals during clinical trials worldwide. Of these, 4326 patients have been treated for at least 3 months, 3407 patients have been treated for at least 6 months, 2150 patients have been treated for 1 year, 1250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 2809 patients were exposed to doses of 10-12 mg, 2615 patients treated for 3 months, 2328 patients treated for 6 months, 1378 patients treated for 1 year, 917 patients treated for 2 years, and 129 treated for over 3 years.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa, and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paraesthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goitre, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, dermatitis contact.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Post-Introduction Reports: Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

Store below 77°F (25°C) in a tight container.

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