

Treatment of fragile X-associated tremor ataxia syndrome (FXTAS) and related neurological problems

Randi J Hagerman^{1,2}
 Deborah A Hall³
 Sarah Coffey^{1,2}
 Maureen Leehey³
 James Bourgeois⁴
 John Gould⁵
 Lin Zhang⁶
 Andreea Seritan⁴
 Elizabeth Berry-Kravis⁷⁻⁹
 John Olichney⁶
 Joshua W Miller¹⁰
 Amy L Fong¹¹
 Randall Carpenter¹²
 Cathy Bodine¹³
 Louise W Gane^{1,2}
 Edgar Rainin¹
 Hillary Hagerman¹
 Paul J Hagerman¹⁴

¹M.I.N.D. Institute, ²Department of Pediatrics, ⁴Department of Psychiatry & Behavioral Sciences, ⁵Department of Urology, ⁶Department of Neurology, ¹⁰Department of Pathology and Laboratory Medicine, ¹⁴Department of Biochemistry and Molecular Medicine, University of California, Davis, School of Medicine, Sacramento, CA, USA; ³Department of Neurology, University of Colorado, Denver, CO, USA; ⁷Department of Pediatrics, Neurology, and Biochemistry, ⁸Department of Neurological Sciences, ⁹Department of Biochemistry, Rush University Medical Center, Chicago, IL, USA; ¹¹Physical Edge, Inc., Davis, CA, USA; ¹²Seaside Therapeutics, Cambridge, MA, USA; ¹³Department of Physical Medicine and Rehabilitation, University of Colorado Health Sciences Center, Denver, CO, USA

Correspondence: Randi J Hagerman
 UC Davis M I N D Institute, 2825 50th
 Street, Sacramento, CA 95817, USA
 Tel +1 916 703 0247
 Fax +1 916 703 0240
 Email randi.hagerman@ucdmc.ucdavis.edu

Abstract: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurological disorder that affects older adult carriers, predominantly males, of premutation alleles (55 to 200 CGG repeats) of the fragile X (*FMRI*) gene. Principal features of FXTAS are intention tremor, ataxia, parkinsonism, cognitive decline, and peripheral neuropathy; ancillary features include, autonomic dysfunction, and psychiatric symptoms of anxiety, depression, and disinhibition. Although controlled trials have not been carried out in individuals with FXTAS, there is a significant amount of anecdotal information regarding various treatment modalities. Moreover, there exists a great deal of evidence regarding the efficacy of various medications for treatment of other disorders (eg, Alzheimer disease) that have substantial phenotypic overlap with FXTAS. The current review summarizes what is currently known regarding the symptomatic treatment, or potential for treatment, of FXTAS.

Keywords: fragile X syndrome, dementia, ataxia, neurodegeneration, parkinsonism, tremor

Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is seen in a subgroup of older adults who are carriers of premutation alleles (55–200 cytosine, guanine and guanine [CGG] repeats) of the fragile X mental retardation 1 (*FMRI*) gene (Hagerman et al 2001; Berry-Kravis et al 2007; Jacquemont et al 2007; Leehey et al 2007). The pathogenesis of FXTAS results from the direct neural cell toxicity of elevated levels of the expanded-CGG-repeat *FMRI* mRNA (RNA toxic gain-of-function), which leads in turn to dysregulation of a number of proteins including lamin A/C and alpha B crystallin (Arocena et al 2005). Characteristic neuropathological findings of FXTAS include formation of inclusions in neurons and astrocytes throughout the brain; spongiform white matter changes in subcortical, periventricular and brainstem regions, including the middle cerebellar peduncles (MCP sign); and global brain atrophy (Greco et al 2002; Jacquemont et al 2003; Cohen et al 2006; Greco et al 2006). The natural history of FXTAS begins with the onset (average age, 60 yr) of a movement disorder involving intention tremor and/or gait ataxia with tremor often preceding the ataxia by one to several years (Leehey et al 2007). Decline in mobility generally progresses through the use of a cane, walker, and wheelchair, with eventual inability to ambulate (Leehey et al 2007). FXTAS also includes neuropathy in the majority of patients, often involving pain, particularly in the lower extremities (Jacquemont et al 2004; Berry-Kravis et al 2007; Hagerman et al 2007).

Additional features include autonomic dysfunction involving impotence, hypertension, orthostatic hypotension, urinary frequency, and urinary and bowel incontinence (in the later stages). Psychiatric problems commonly seen in patients with FXTAS include anxiety, agitation, apathy, and depression (Bacalman et al 2006). However,

a subgroup of premutation carriers may have psychiatric problems even in childhood or adolescence, with features that can include ADHD, obsessive/compulsive thinking, anxiety disorders, or social difficulties (Cornish et al 2005; Farzin et al 2006; Hessler et al 2006). Cognitive changes in patients with FXTAS include executive function deficits and memory problems, which may be present at the time the individual is diagnosed with tremor and/or ataxia (Grigsby et al 2006, 2007). The cognitive changes progress at a variable rate and dementia develops in at least 50% of cases (Bourgeois et al 2007).

Premutation alleles of the *FMRI* gene are relatively common in the general population, carried by ~1 in 130–250 females and ~1 in 500–800 males (Rousseau et al 1995; Pessio et al 2000; Dombrowski et al 2002; Beckett et al submitted). FXTAS occurs in older carriers (>50 years), is more common in males, and has age-dependent penetrance: 17% in their 50s, 38% in their 60s, 47% in their 70s, and 75% in their 80s (Jacquemont et al 2004). These numbers lead to an estimated prevalence of FXTAS as approximately 1 in 8,000 males over 50 years in the general population (Jacquemont et al 2004, 2007). A recent study in female carriers suggests that 4% overall and 8% over 50 years of age develop FXTAS, but it has a milder course than in males, perhaps related to a protective effect of the second (normal) X chromosome in females (Jacquemont et al 2004; Coffey et al in press).

Recent studies have broadened our concept of FXTAS to include hormonal dysfunction. Inclusions have been documented in the anterior and posterior pituitary (Louis et al 2006; Greco et al 2007), and in the Leydig cells in the testicles, which produce testosterone. In one study, testosterone deficiency was reported in 5 of 8 carriers that were tested, with such reductions presumably related to the pituitary and Leydig cell involvement (Greco et al 2007). Additional hormonal problems including hypothyroidism are seen in approximately 50% of women with FXTAS (Coffey et al in press). Fibromyalgia is seen in 40% of women with FXTAS, although the pain associated with that patient description may be difficult to distinguish from painful neuropathy (Coffey et al in press).

It has been known since 1991 that approximately 20% of women with the premutation have premature ovarian failure (Cronister et al 1991), with the frequency of this finding more recently shown to correlate with the size of the CGG expansion in the premutation range (Sullivan et al 2005). Features of FXTAS, including age of onset of tremor and ataxia (Tassone et al 2007), severity of both tremor and ataxia, overall motor impairment (Leehey et al 2007),

severity of brain atrophy, and white matter disease (Loesch et al 2005; Cohen et al 2006), the density of inclusions and the age of death (Greco, Berman et al 2006), all correlate with the CGG repeat number.

The diagnosis of FXTAS is made clinically utilizing criteria set forth in Jacquemont and colleagues (2003) which can be seen in Table 1. Definite FXTAS requires the presence of the major radiological sign, white matter disease in the MCP, in addition to tremor and/or ataxia in a premutation carrier. On autopsy, the presence of eosinophilic (ubiquitin-positive; tau-, synuclein-negative) inclusions in the nuclei of neurons and astrocytes is also characteristic of definite FXTAS, and has been added to the diagnostic criteria (Hagerman and Hagerman 2004). However, the MCP sign is only seen in 60% of males with FXTAS (Cohen et al 2006), and in approximately 13% of females with FXTAS (Adams et al 2007). Individuals with the premutation with tremor and ataxia but without the MCP sign (including those who have not had an MRI or cannot have an MRI) are described as probable FXTAS. Those with fewer symptoms, such as tremor or ataxia only, are described as possible FXTAS (Table 1).

Table 1 Clinical diagnostic criteria for FXTAS (Adapted from Jacquemont et al 2003)

Molecular	CGG repeat 55–200	
Clinical		
Major	Intention tremor Gait ataxia	
Minor	Parkinsonism Moderate to severe short term memory deficiency Executive function deficit	
Radiological		
Major	MRI white matter lesions involving middle cerebellar peduncles	
Minor	MRI white matter lesions involving cerebral white matter Moderate to severe generalized brain atrophy	
Diagnostic categories		
Definite	Probable	Possible
One major clinical, And either One major radiological, or Presence of intranuclear inclusions (Hagerman and Hagerman 2004)	Two major clinical; or One minor clinical, and One major radiological	One major clinical, and One minor radiological

Abbreviations: FXTAS, fragile X-associated tremor ataxia syndrome; CGG, cytosine, guanine and guanine; MRI, magnetic resonance imaging.

There is currently no targeted therapeutic intervention that can arrest or reverse the pathogenesis of FXTAS; however, there are a number of treatment approaches of potential symptomatic benefit, and these are reviewed here. Moreover, there are neuroprotective agents that may slow the course of FXTAS. We emphasize that no randomized, controlled clinical trials have yet been carried out specifically in individuals with FXTAS for any therapeutic agent or procedure, given its relatively recent discovery. Therefore, the current review must be considered as a summary of experiential reports by patients with FXTAS and their medical providers, or as summaries of the efficacies of agents/procedures that have proven to be effective in other disorders that have significant symptom overlap with FXTAS (Jacquemont et al 2004; Bourgeois et al 2006; Hall et al 2006). Clearly, what is necessary at this point is to establish controlled clinical trials for these interventions in patient populations with FXTAS.

Treatment of tremor

Fifty-six patients with FXTAS completed a questionnaire to determine if any medications had been effective for neurological symptoms (Hall et al 2006). This was followed by a record review of treatment of their neurological symptoms. Although 70% of patients with definite FXTAS were on medications for their neurological symptoms, only 30% of patients with possible or probable FXTAS were taking medications for motor signs (tremor, ataxia, or parkinsonism). Of the subjects receiving therapy for action tremor; 3/6 reported mild to moderate improvement on primidone, 3/8 had moderate improvement of tremor on beta-blockers, 2/8 had moderate improvement on benzodiazepines. One subject had improved tremor on memantine, which was prescribed for cognitive decline. There was no improvement in tremor for two subjects on gabapentin.

Beta-blockers and primidone are commonly used to treat essential tremor (ET) and may be the most likely candidates for initiating therapy in FXTAS. Because controlled studies have not been carried out in FXTAS, we discuss data from the ET treatment literature. Propranolol, a β -adrenergic blocker, is the most effective medication for the treatment of ET and may help enhanced physiologic tremors as well (Caccia et al 1989; Calzetti et al 1990); however, these medications are contraindicated in patients with asthma, second-degree AV block, and insulin dependent diabetes. Fatigability, impotence, lightheadedness, sedation and depressive symptoms are common side effects. Primidone has also been shown to be effective in placebo controlled studies in ET (Koller and Royse 1986), with its anti-tremor effect attributed to its

metabolite phenobarbital (Sasso et al 1991). It is started at low doses (eg, 25 mg/day or less), to minimize side effects such as nausea, vomiting, sedation, worsening of motor coordination, and confusion. If propranolol and primidone are not beneficial, second line treatment includes topiramate, an anti-convulsant with tremor efficacy in placebo-controlled trials. Sotalol, atenolol (other beta-blockers that may have less side effects than propranolol), and alprazolam, a benzodiazepine that is also reported to be effective in some patients, may also be considered (Gunal et al 2000). Because tremor is exacerbated by anxiety or stress in most disorders, benzodiazepines may help to reduce anxiety and reduce tremor secondarily. If these treatments fail, other medications that may be helpful and have shown some effectiveness in open-label trials include botulinum toxin, levetiracetam (Bushara et al 2005), clonazepam, clozapine, nadolol, and nimodipine (Zesiewicz et al 2005). In a single open-label study levetiracetam was found to be helpful for cerebellar tremor (Striano et al 2006). The latter is relevant for FXTAS because cerebellar dysfunction is a prominent finding in many affected persons.

In Hall and colleagues (2006), rest tremor was not evaluated exclusively, but FXTAS patients with parkinsonism (rest tremor, slowness, or stiffness) improved on carbidopa/levodopa in 4/10 subjects, pramipexole in 3/6 subjects, and in one patient on eldepryl (Hall et al 2006). Although parkinsonism is considered a minor criteria for FXTAS, some patients are dopamine responsive making them similar to patients with idiopathic Parkinson disease. It is unknown whether motor fluctuations, dyskinesia, or other side effects of these medications occur in patients with FXTAS, but dopaminergic therapy should be considered if parkinsonism is problematic in a patient with FXTAS.

Botulinum toxin injections

Botulinum toxin (BTX) is most commonly used in treating conditions that involve involuntary muscle activities, such as dystonia and spasticity. Its indications, though not all yet approved, have expanded during recent years, to include its use in the management of oversecretion of sweat glands, hypersalivation, and tremors (Cordivari et al 2004). On a trial basis, we applied BTX in one of our patients with FXTAS with a disabling arm tremor. Under the guidance of electromyography (EMG), 10–15 units of Botox (the type A of BTX, BTX A) were injected into flexor digitorum superficialis, flexor digitorum profundus, and extensor digitorum. The exact dosage of BTX injected was determined based on the real-time activities shown on EMG, which provides anatomical guidance for injections. The injection protocol

was repeated every three months on average. The patient experienced significant functional improvement following the injections, with reduced tremor during action and at rest one week later. The maximal effect of BTX was experienced at 4–6 weeks post injections, and benefit lasted up to three months on average.

Placebo controlled trials of BTX in essential tremor have shown that in some cases there is significant reduction of tremor amplitude, but only mild functional improvement associated with problematic limb weakness (Jankovic et al 1996; Brin et al 2001; Cordivari et al 2004). Faced with the challenge of medical management of the disabling tremor in patients with FXTAS, further study in this disorder, including controlled trials, are warranted.

Deep brain stimulation

Only three persons with FXTAS that underwent bilateral thalamic deep brain stimulation for tremor have been reported (Leehey et al 2003; Peters et al 2006). In one, a transient microthalamotomy effect improved tremor greatly but speech was softer and gait ataxia worsened markedly (Leehey et al 2003). Tremor reoccurred in four months, and stimulation then was not beneficial due to an open circuit on one side and suboptimal electrode placement on the other. The electrodes were not corrected because of concern that further surgery may worsen speech and ataxia. There was no long-lasting cognitive dysfunction from the surgery. The two other people were cousins (Peters et al 2006). No informative clinical data were available on one; the other had a marked reduction in tremor while gait ataxia persisted postoperatively. This latter patient had mild executive dysfunction prior to surgery and there was no mention about any changes in his mentation postoperatively.

Given these reports suggesting gait ataxia may worsen after surgery, the usefulness of this procedure in FXTAS may be limited. Moreover, persons with preexisting cognitive dysfunction tend to dement after bilateral deep brain stimulation (Aybek and Vingerhoets 2007), and persons with FXTAS frequently have significant cognitive dysfunction, further dampening enthusiasm for using this procedure in this population. However, persons with little or no ataxia or cognitive deficits, but with disabling medically resistant tremor may still be candidates, at least for unilateral surgery, which is less likely to worsen ataxia and cognition than bilateral surgery.

Computer modifications

Several approaches to the problem of the use of the computer mouse by individuals with essential tremor have been

tried with varying degrees of success. One is to reduce the physical tremor by mechanical means, such as adding mass and/or some form of damping to the mouse. Although this can be helpful for some people, such a mouse can be physically tiring to use. Furthermore, it is difficult to adjust the mass and damping to a particular individual's needs, which may vary over time and circumstance. A second approach is to use a different type of pointing device, such as a trackball, job stick, or keyboard keys. This helps some people, but not others. For example, using a trackball requires good finger dexterity, while certain types of joysticks can actually increase the tremor. A third approach, which was taken in a study completed at the University of Colorado Health Sciences Center, is to accept the mouse motion and apply a digital smoothing algorithm to reduce its effects. Researchers at the IBM Watson Research Center created the Assistive Mouse Adapter (www.montrosesecan.com) algorithm which has demonstrated a positive difference in cursor movement, button clicking, and speed of use in patients with tremor although none had FXTAS (Bodine et al 2007).

Treatment of ataxia

Gait difficulties may be caused by cerebellar ataxia or parkinsonism in FXTAS and can be exacerbated by peripheral neuropathy. In those with parkinsonism and gait abnormalities, subjective improvement was seen on carbidopa/levodopa, dopamine agonists, and eldepryl as mentioned above (Hall et al 2006). Ataxia improved in one patient on amantadine in the Hall and colleagues (2006) report and in two patients reported by Jacquemont and colleagues (2004). There is no universally effective treatment for cerebellar ataxia, but a small proportion of subjects on amantadine or buspirone will show improvement. Unfortunately, these medications may be poorly tolerated in ataxia patients (Hassin-Baer et al 2000).

In addition to pharmacological treatment, physical therapy can be helpful for improving strength and gait in treatment of patients with ataxia and parkinsonism, particularly as these patients continue to age (Ellis et al 2005; Cao et al 2007). Patients with cerebellar ataxia tend to exhibit gait abnormalities including slower walking velocity with reduced step length and high variability in step timing and amplitude (Ebersbach et al 1999). Researchers have found that the variability in gait speed is more attributable to balance-related deficits than intra-limb coordination of leg placement during walking (Morton and Bastian 2003; Ilg et al 2007). Traditionally, patients with Parkinsonism have responded well to step and gait training in physical therapy.

Lasting improvements in overground walking speed, stride length, cadence, and fall reduction have been seen with physical therapy and particularly with body-weight-supported treadmill training (Miyai et al 2002; Pohl et al 2003; Protas et al 2005). In our experience these approaches have been helpful for individuals with FXTAS, but no studies of efficacy have been reported yet.

Treatment of cognitive deficits and dementia

The treatment of cognitive impairment in FXTAS is based on off-label application of dementia treatments conventionally used in Alzheimer's disease (Farlow and Cummings 2007). Cautious dosing of donepezil and other cholinesterase inhibitors can be considered for the memory impairment; in the early weeks and months of treatment memory function may be enhanced. Even if the eventual course of memory and other cognitive decline is not substantially altered, short-term improvement in quality of life can result (Bourgeois et al 2006). In addition, the frequent co-morbidities of depressive, anxiety, and psychotic disorders may lead the clinician to treat with antidepressants and/or antipsychotics. The positive treatment effects on mood, anxiety, and psychosis can also result in improved cognitive symptoms and performance as seen in a case report of FXTAS (Bourgeois et al 2006). Anecdotal information also suggests that memantine, which may decrease glutamate-mediated neurotoxicity (Choi et al 1988), is helpful in FXTAS, but controlled studies have not been carried out. Memantine is typically well tolerated when started at low-dose (ie, 5 mg every morning) with a gradual increase to 10 mg twice a day (Reisberg et al 2003). Randomized trials are currently being planned for cholinesterase inhibitors, memantine, and other putatively neuroprotective (eg, lithium) agents to address the effect of these medications on both the clinical symptoms and the eventual prognosis for the cognitive aspects of FXTAS (Bauer et al 2003; Chuang 2004).

While it has yet to be established in clinical trials, using the example of other neurodegenerative diseases (Scarmeas et al 2005; Aggarwal et al 2006), it may be that progression in the motor symptoms predicts similar deterioration in the cognitive symptoms. Thus, clinicians should be particularly vigilant for cognitive symptoms if the tremor and ataxia symptoms are in a period of progression.

Evaluation for other causes of dementia, particularly reversible contributing causes, such as hypothyroidism, HIV, syphilis, B12 deficiency, thiamine, B6, or folate deficiency, is essential. Patients with FXTAS will usually have significant

brain atrophy with dilatation of the ventricles, which may be mistaken for normal pressure hydrocephalus (NPH). However, surgery for presumed NPH has been disastrous in cases of FXTAS (Jacquemont et al 2004). Typically patients with FXTAS do not tolerate surgery with general anesthesia well and further deterioration in both motor and cognitive abilities is typically seen (Jacquemont et al 2004). Therefore, surgery should be avoided if at all possible. Support for family caretakers during the dementia process is crucial, and the decision to place a patient with FXTAS in a center that delivers specialty care for dementia patients is often eventually necessary in late-stage disease.

Nutrition and exercise studies in related conditions

Many studies have investigated the possible role of diet and exercise in Alzheimer's disease (AD), dementia, and related conditions. It is likely that the deficiencies discussed here will impact patients with FXTAS just as they do other causes of dementia. Deficiencies in B vitamins, particularly folate and vitamin B12, are common in elderly populations and have been associated with increased risk of cognitive impairment and dementia (Clarke et al 1998; Ramos et al 2005; de Lau et al 2007; Durga et al 2007). Of particular interest is the sulfur amino acid homocysteine, which becomes elevated in the blood (hyperhomocysteinemia) when folate or vitamin B12 is deficient (Selhub and Miller 1992). Hyperhomocysteinemia is an independent risk factor for vascular disease, including cerebrovascular disease (Refsum et al 1998), and is associated with both an increased prevalence and incidence of AD and dementia (Clarke et al 1998; Miller et al 2002; Seshadri et al 2002; Haan et al 2007). Lowering plasma homocysteine levels with B vitamin supplements may reduce the risk, though clinical trials are necessary to determine if such interventions will ultimately benefit patients with FXTAS or AD (Luchsinger et al 2007). It may be the case that preventing hyperhomocysteinemia before cognitive deficits appear will be more beneficial than intervening after cognitive impairment has been manifested.

Alternatively, deficiencies of folate and vitamin B12 may have effects on brain function independent of homocysteine. Both vitamins are involved in the synthesis of S-adenosylmethionine (SAM), which serves as the universal methyl donor for a wide variety of methylation reactions, including those involving neurotransmitters, membrane phospholipids, myelin, and DNA (Selhub and Miller 1992). Of note is that both folate and vitamin B12 deficiencies have been associated with depression (Alpert and Fava 1997),

and oral supplements of SAM have been shown to alleviate depressive symptoms (Mischoulon and Fava 2002). There is also some evidence that folate has antioxidant properties (Stanger et al 2002), though this is not currently considered a major property of the vitamin. Nonetheless, neurons with the FXTAS premutation will die more easily with oxidative stress, and we recommend folate and B complex supplementation (to avoid deficiencies). However, the prevalences of folate, vitamin B12, and other B vitamin deficiencies, as well as hyperhomocysteinemia in FXTAS patients are not well-documented and it is unknown if B vitamin supplements in FXTAS patients will protect against the cognitive impairment and depression associated with the disorder.

Other dietary factors may be important in FXTAS. Treatment with antioxidants, such as vitamins C and E, may help prevent and treat the oxidative damage in neuronal cells (Sano 2003).

Exercise can also affect the outcomes of patients with AD, FXTAS, and other neurodegenerative diseases and it can stimulate neurogenesis. Aerobic exercise has been found to modify cognition, such as executive functioning, and reduce symptoms of depression and behavioral problems in AD patient populations (Yu et al 2006; Rolland et al 2007). We recommend exercise for patients with FXTAS, because in our clinical experience it has been helpful. An exercise routine that includes walking, strength, balance, and flexibility training may be therapeutic (Rolland et al 2007). For patients experiencing significant tremor, this should be guided by a physical therapist, as described above.

Treatment of psychiatric problems

Psychiatric problems can occur prior to the onset of FXTAS, and include ADHD, anxiety disorders, and depression in a subgroup of carriers. Females have been studied to the greatest extent, although the stress of raising a child with fragile X syndrome may exacerbate any underlying pathology related to the premutation (Franke et al 1996, 1998). The limbic system has a higher transcription rate for the *FMR1* mutation than most other areas of the brain and therefore it may be the most vulnerable to the RNA toxicity effect of the premutation (Hagerman and Hagerman 2004; Tassone et al 2004). Recent evidence of the association of depression with Alzheimer disease suggests that early treatment of psychiatric problems, particularly depression and anxiety, which can lead to neuronal cell death in the hippocampus, should be treated early (Sapolsky 2000). This is likely true for all brain diseases but there is a predisposition to depression in individuals with the premutation even before the onset of

FXTAS (Franke et al 1996; Hagerman and Hagerman 2002; Hessel et al 2005). In addition, the use of selective serotonin reuptake inhibitors (SSRIs) to treat depression or anxiety can stimulate neurogenesis in the aging brain and may therefore be neuroprotective for later cognitive decline (Jacobs et al 2000; Santarelli et al 2003). Neurogenesis, the making of new neurons in adulthood, only occurs in the olfactory bulb and in the dentate gyrus of the hippocampus. The latter is important for learning and memory (Jacobs et al 2000). A stimulating environment that includes regular exercise may enhance neurogenesis, but increased stress or increased levels of glucocorticoid hormones (cortisol) is expected to inhibit neurogenesis (Jacobs et al 2000). Therefore teaching patients to reduce stress and increase exercise as described above may be beneficial for neurogenesis and may be particularly helpful in patients with FXTAS.

Integrated psychopharmacological approaches with antidepressants and antipsychotics (if needed) along with cognition enhancers (discussed above) are indicated. Among antidepressants, tricyclics (TCAs) and MAOIs have a propensity for systemic side effects (anticholinergic effects of TCAs may also further compromise cognition) and are best avoided. SSRIs with minimal drug-drug interaction profiles (eg, sertraline, citalopram, escitalopram) are preferred; paroxetine, fluoxetine, and fluvoxamine are discouraged due to drug-drug interaction risk. The selective serotonin norepinephrine reuptake inhibitors (SNRIs; venlafaxine and duloxetine) are to be considered, as their noradrenergic activity may be desirable. Duloxetine may have the added benefit of reducing pain as described below. Both of these medications are used only with caution in renal failure, and they have CYP2D6 inhibitory effects so there can be interactions with other medications. Mirtazapine is helpful especially for sedation and appetite stimulation; its dose is usually decreased in renal failure. For psychotic symptoms, cautious use of atypical antipsychotics is recommended with close follow-up; olanzapine is problematic in diabetes, while ziprasidone can be problematic in patients with increased QTc. There have been no cases of serious cardiac events with any of the atypical antipsychotic drugs (Tandon 2002; Harrigan et al 2004). The newer antipsychotic, aripiprazole, may have the least metabolic side effects and may be a useful choice when needed in patients with FXTAS.

Treatment of autonomic dysfunction

Urinary urgency and frequency can be irritating symptoms, starting in the early 40's and slowly become debilitating as

the FXTAS patient ages. The normal micturition rate for most men is about every three hours with average fluid intake but may progress to every 20 minutes in severely affected individuals. Micturition is associated with difficulty starting the stream, difficulty emptying the bladder and dribbling. Detailed urodynamic studies have not been conducted, but hyperactive detrusor activity is possible since some patients respond well to tricyclic antidepressants or muscarinic receptor antagonists. Patients who do not respond well to this therapy may be experiencing poor bladder contractility or sphincter dyssynergia. In many patients a more effective treatment is cystoscopy under local anesthetic with injections of 200 cc of Botox into the submucosal lining of the bladder in 10 cc aliquots. If a small diameter cystoscope is used the procedure is relatively well tolerated. A rare patient will develop an inability to urinate, and self-catheterization can easily be taught. After Botox injections patients are treated with an antibiotic and infections are rare. Mild hematuria usually resolves within 3 to 5 days. The effects of the botulinum can last from 3 to 4 months or longer.

Bowel incontinence is a late effect of FXTAS and may start as a slowly progressive dilated and tortuous large bowel and result in chronic megacolon as the patient ages. No definitive research has been done on patients with FXTAS but it is presumed that autonomic anomalies are responsible for these signs and symptoms as well as overactive bladder (OAB). The treatment of chronic megacolon is laxatives to prevent constipation and high fiber supplements to encourage normal peristalsis. A new laxative regimen that is usually reserved for short 1–2 week treatments consists of polyethylene glycol (17 g in 250 cc of fluid) once or twice a day, which may need to be used for up to a year. Side effects of diarrhea might require modifying the dose. The medication is not absorbed by the small bowel or colon but acts as an osmotic laxative bringing water into the bowel and softening the stool. The rationale behind the treatment is to slowly train the bowel to constrict down to a more normal size. Further studies of this problem in FXTAS are warranted.

Swallowing difficulties are a common, typically late symptom in FXTAS. We have seen one recent case of FXTAS with swallowing difficulties who had an excellent response to pyridostigmine bromide, a reversible acetylcholinesterase inhibitor, which is typically used to enhance muscarinic signal transmission in the management of myasthenia gravis. Adverse effects are from stimulation of the parasympathetic nervous system via muscarinic receptors and they can include sweating, salivation, nausea, vomiting, diarrhea and abdominal cramping.

Pyridostigmine can also be used for orthostatic hypotension (Gales and Gales 2007), which is also common in FXTAS. It also enhances sympathetic signal transduction, which increases peripheral vascular resistance and increases baroreceptor sensitivity, which helps with orthostatic symptoms without exacerbating supine hypertension. Other agents that may be helpful in some cases for patients with FXTAS and orthostatic hypotension, include those often used in patients with multiple system atrophy or Parkinson disease such as midodrine and fludrocortisone. Increasing fluid and salt intake can also be helpful if there are no medical contraindications (eg, coexisting heart disease or hypertension).

Systemic hypertension is seen in the majority of both male and female patients with FXTAS (Jacquemont et al 2003; Coffey et al in press), and it is thought to be related to autonomic dysfunction. It is often seen early, prior to the onset of tremor and or ataxia. Because hypertension can lead to hypertensive encephalopathy, it is important to treat it early to avoid any exacerbation of CNS disease related to FXTAS.

Treatment of hormonal dysfunction

Hypothyroidism is a common problem among females with the premutation. A recent study demonstrated that 17% of adult women with the premutation had thyroid dysfunction, usually hypothyroidism, while 50% of women who had FXTAS had thyroid dysfunction, and this was significantly different from aged matched controls without the premutation (Coffey et al in press). Therefore, routinely testing for thyroid dysfunction is indicated on a yearly basis in women with the premutation who are older than 50 years and particularly those who have neurological problems. Replacement is indicated for hypothyroidism because if left untreated cognitive deficits may occur, and psychiatric problems could be amplified over those that may already be present in premutation carriers (Devdhar et al 2007).

We have noted testosterone deficiency in some patients with FXTAS, although no large studies have been conducted (Greco et al 2007). We have even seen affected individuals become aware of erectile dysfunction before the onset of other neurological signs. Low testosterone is only one of many causes of male impotence, but it is logical to speculate that testosterone replacement may improve libido and sexual function in FXTAS patients. Other problems associated with FXTAS which might improve include cognition, memory, energy level and mood (Cherrier et al 2003; Hagerman and Hagerman 2004). Further studies of testosterone deficiency in FXTAS are warranted and the benefits of testosterone replacement require study.

Treatment of pain

Pain is a common problem in patients with FXTAS and it includes neuropathic pain, particularly in the lower extremities seen in both males and females (Hagerman et al 2007), and fibromyalgia pain which is more common in females with FXTAS (Coffey et al in press). Although neuropathic pain is difficult to treat, available pharmacologic treatments provide meaningful relief for many patients. Neuropathic pain is typically refractory to acetaminophen and nonsteroidal anti-inflammatory drugs. Effective treatments include antidepressants, antiepileptics, and topical analgesics (Gilron et al 2006). In our experience, treatment with gabapentin or pregabalin has proven beneficial for patients with FXTAS and neuropathic pain. In addition, application of Lidoderm (lidocaine 5%) patches can provide symptomatic relief for peripheral neuropathic pain in the lower extremities (Herrmann et al 2005). Up to three patches can be applied over intact skin on the affected areas and left in place for up to 12 hours over a 24-hour period. Fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome occur commonly in female subjects with FXTAS (Coffey et al in press). There is no clear separation of these syndromes, which are often co-morbid with mood disturbances. Initial treatment for fibromyalgia should include nonpharmacologic treatments such as cardiovascular exercise, cognitive-behavioral therapy and/or structured patient education (Goldenberg et al 2004). The most effective pharmacologic treatments include antidepressant, anticonvulsant and/or muscle relaxant medications (Goldenberg et al 2004). If the above treatments do not provide acceptable pain relief, patients should be referred to a pain specialty clinic for consideration of interventional treatments, pain rehabilitation programs and/or chronic treatment with potent opioid analgesics.

Massage therapy

Tremors can be exacerbated by anxiety and stress, as noted earlier, so an important approach to treatment of these symptoms would be the reduction of these tremor stimulators. Massage has been shown to be effective in reducing cortisol levels, stress and anxiety, as well as improving overall mental health (Balint et al 2002; Mannerkorpi and Henriksson 2007; Sharpe et al 2007; Tsao 2007). Pain and discomfort, also associated with fibromyalgia, stiffness (eg, with parkinsonism), and fatigue are also contributors to stress and anxiety. Massage therapy can lessen these types of discomforts, as well as decrease uncomfortable sleep movements and lengthen the sleeping span (Field et al 2002). A recent study demonstrated efficacy with acupuncture/pressure

point massage versus Swedish massage in improving pain in fibromyalgia and chronic pain conditions (Tsao 2007). In 2007, Mannerkorpi and Henriksson (2007) demonstrated a controlled trial of pain relief with massage. Neuromuscular therapies (NMT) have shown efficacy when treating motor symptoms like spasticity and rigidity, which can occur in FXTAS (Svircev et al 2005). This type of therapeutic approach may also help with gait difficulties seen in FXTAS. For the elderly, massage therapies are an important alternative or additive therapy to pharmacological agents described above, particularly when side effects of medications are problematic (Sharpe et al 2007).

Psychosocial approaches

Psychoeducation, supportive intervention for the patient and their family, and delivering psychiatric care in the context of a multidisciplinary team, are all helpful approaches. Given the fact that several members in the same family are often affected, the intervention may target the patient and the family, with consistent longitudinal follow-up being a critical component.

Problem-solving therapy (PST) is a therapeutic modality which has been shown to improve depressive symptoms and functioning in depressed elderly patients with executive dysfunction, and cognitively unimpaired, depressed elderly and adults with minor and major depression in the primary care setting (Arean et al 1993; Unutzer et al 2002; Alexopoulos et al 2003; Haverkamp et al 2004; Steffens et al 2006). In the last decade, strong empirical evidence has been gathered to support this novel psychotherapy type (Mackin and Arean 2005). Problem-solving therapy may be used in FXTAS patients without dementia, as they have significant executive function deficits (Grigsby et al 2007). Executive dysfunction increases the risk of poor response of geriatric depression to medications (Alexopoulos et al 2005). By addressing the executive dysfunction, the patients' daily functioning may improve and their response to antidepressants will be amplified. Furthermore, the caregivers' wellbeing may be enhanced along with the patients' mood and anxiety symptoms. Women constitute the majority of caregivers for patients with FXTAS and 70% of the care-giving population. Women were found to have significantly higher odds than male caregivers of having a high score on the Zarit Burden Interview (ZBI). Poor perceived physical health and more behavior disturbance in the patient were associated with higher odds of high levels of caregiver burden and depression (Gallicchio et al 2002). In our clinical experience depression is very common in the wives of men with FXTAS and they typically do well with

supportive counseling and the addition of an SSRI agent for treatment of their depression.

Genetic counseling

Genetic counseling for FXTAS is complicated. In addition to the genetic information and obtaining the family pedigree, there are many psychosocial features to be addressed that are, themselves, a consequence of the neuropsychiatric features (Bourgeois et al 2006; Grigsby et al 2006). When addressing the family history, questions regarding neurological, immunological, and endocrine issues must be asked in addition to a family history of mental impairment, autism, ADHD, behavioral and emotional problems. It is suggested that the family history be obtained from the spouse of the patient with FXTAS as the patient is likely to be overwhelmed with too much information and with recommendations that affect quality of life, such as the cessation of driving or need for a cane, walker or wheelchair. In addition, the patient may not be aware of the severity of his FXTAS-related clinical findings and find it depressing and threatening to have these addressed. Impotency and incontinence also have the potential to threaten self-esteem and the genetic counselor needs to be aware of and sensitive to all these issues.

The patient with FXTAS cannot be treated in isolation. The questions, concerns, and needs of the caregiver/spouse must be addressed, as Bacalman and colleagues (2006) has shown that these individuals experience varying degrees of stress. Therefore, we recommend meeting with the caregiver separately from the patient in order to obtain a more accurate understanding of the patient's condition and progression and to explore the caregiver's emotional state and understanding of FXTAS. As in Alzheimer disease, the caregiver is prone to depression, feelings of being overwhelmed, grief over the loss of a planned future, anger regarding the irritability and lack of support from the patient, and a lack of understanding of what the future needs of the patient may be (Bacalman et al 2006). The caregiver should be encouraged to maintain their own network of friends and activities outside of the home so they develop independence and an identity beyond that of caregiver. Additionally, the issues of long-term care must be addressed with the caregiver/spouse as they often are not be addressed by the primary care provider.

It is important to end the visit with both the patient and caregiver present in order to summarize their individual understanding of the issues and to help them to be supportive of each other. Mutual intimacy, sensitivity and independence should be encouraged as they work in partnership to address FXTAS. Often, a genetic counselor must be willing to address these areas.

Conclusions and future directions

A number of medications and therapies have been noted to be helpful for the symptoms of FXTAS, although no controlled trials of efficacy have been carried out. Therefore, it is critical that controlled trials be undertaken with existing therapeutic agents or modalities where anecdotal evidence in patients with FXTAS, or controlled studies with related disorders, suggests that such approaches would be efficacious.

Since FXTAS is a progressive neurodegenerative disorder, and because none of the current therapies target FXTAS pathogenesis, such approaches will, at best, stall or transiently improve the symptoms of the disorder. Therefore, development of therapeutic interventions that target the core molecular processes that underlie FXTAS is essential. Such therapeutics would, in principle, target either the pathogenic trigger, the expanded-CGG-repeat mRNA itself ("toxic RNA"), or downstream pathways that are altered as a consequence of the abnormal *FMR1* mRNA expression. Whereas the simplest approach, conceptually, would be to use antisense or RNA interference methods to knock down the pathogenic RNA itself, such approaches remain difficult due to the general inability of such agents to traverse the blood brain barrier. However, as we learn more about the other molecular abnormalities, and proteins involved, with the downstream pathways (Jin et al 2004; Arocena et al 2005; Iwahashi et al 2006), additional opportunities for targeted interventions will hopefully become available.

Acknowledgment

This work was supported by grants from the Coleman Foundation, National Institutes of Health HD036071, HD02274, NS044299, NS052487, UL1RR024922, RL1AG032115, and Centers for Disease Control and Prevention U10/CCU925123. The authors report no other conflicts of interest.

References

- Adams J, Adams P, Nguyen D, et al. 2007. Volumetric brain changes in males and females with the fragile X associated tremor/ataxia syndrome (FXTAS). *Neurology*, 69:851–9.
- Aggarwal NT, Wilson RS, Beck TL, et al. 2006. Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. *Arch Neurol*, 63:1763–9.
- Alexopoulos GS, Kiosses DN, Heo M, et al. 2005. Executive dysfunction and the course of geriatric depression. *Biol Psychiatry*, 58:204–10.
- Alexopoulos GS, Raue P, Areán P. 2003. Problem-solving therapy versus supportive therapy in geriatric major depression with executive dysfunction. *Am J Geriatr Psychiatry*, 11:46–52.
- Alpert JE, Fava M. 1997. Nutrition and depression: the role of folate. *Nutr Rev*, 55:145–9.
- Areán PA, Perri MG, Nezu AM, et al. 1993. Comparative effectiveness of social problem-solving therapy and reminiscence therapy as treatments for depression in older adults. *J Consult Clin Psychol*, 61:1003–10.

- Arocena DG, Iwahashi CK, Won N, et al. 2005. Induction of inclusion formation and disruption of lamin A/C structure by premutation CGG-repeat RNA in human cultured neural cells. *Hum Mol Genet*, 14:3661–71.
- Aybek S, Vingerhoets FJ. 2007. Does deep brain stimulation of the subthalamic nucleus in Parkinson's disease affect cognition and behavior? *Nat Clin Pract Neurol*, 3:70–1.
- Bacalman S, Farzin F, Bourgeois JA, et al. 2006. Psychiatric phenotype of the fragile X-associated tremor/ataxia syndrome (FXTAS) in males: newly described fronto-subcortical dementia. *J Clin Psychiatry*, 67:87–94.
- Balint PV, Kane D, Hunter J, et al. 2002. Ultrasound guided versus conventional joint and soft tissue fluid aspiration in rheumatology practice: a pilot study. *J Rheumatol*, 29:2209–13.
- Bauer M, Alda M, Priller J, et al. 2003. Implications of the neuroprotective effects of lithium for the treatment of bipolar and neurodegenerative disorders. *Pharmacopsychiatry*, 36(Suppl 3):S250–4.
- Beckett L, Yu Q, Long AN. 2008. The impact of Fragile X: Prevalence, numbers affected, and economic impact. A White Paper prepared for the National Fragile X Foundation. September 2005 [online]. Accessed March 5, 2008. URL: <http://www.fragilex.org/Prevalence White Paper Adapted for FQ.pdf>.
- Berry-Kravis E, Abrams L, Coffey SM, et al. 2007. Fragile X-associated tremor/ataxia syndrome: Clinical features, genetics, and testing guidelines. *Mov Disord*, 22:2018–30, quiz 2140.
- Berry-Kravis E, Goetz CG, et al. 2007. Neuropathic features in fragile X premutation carriers. *Am J Med Genet A*, 143:19–26.
- Bodine C, Levine J, Sandstrum J, et al. 2007. Effects of mouse tremor smoothing adapter on ease of computer mouse use by individuals with essential tremor. In: Universal Access in Human Computer Interaction. Coping with Diversity. 4th International Conference on Universal Access in Human-Computer Interaction, UAHCI 2007, Held as Part of HCI International 2007, Beijing, China, July 22–27, 2007, Proceedings, Part I, pp. 632–6.
- Bourgeois JA, Cogswell JB, Hessel D, et al. 2007. Cognitive, anxiety and mood disorders in the fragile X-associated tremor/ataxia syndrome. *Gen Hosp Psychiatry*, 29:349–56.
- Bourgeois JA, Farzin F, Brunberg JA, et al. 2006. Dementia with mood symptoms in a fragile X premutation carrier with the fragile X-associated tremor/ataxia syndrome: clinical intervention with donepezil and venlafaxine. *J Neuropsychiatry Clin Neurosci*, 18:171–7.
- Brin MF, Lyons KE, Doucette J, et al. 2001. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology*, 56:1523–8.
- Bushara KO, Malik T, Exconde RE. 2005. The effect of levetiracetam on essential tremor. *Neurology*, 64:1078–80.
- Caccia MR, Osio M, Galimberti V, et al. 1989. Propranolol, clonidine, urapidil and trazodone infusion in essential tremor: a double-blind crossover trial. *Acta Neurol Scand*, 79:379–83.
- Calzetti S, Sasso E, Baratti M, et al. 1990. Clinical and computer-based assessment of long-term therapeutic efficacy of propranolol in essential tremor. *Acta Neurol Scand*, 81:392–6.
- Cao ZB, Maeda A, Shima N, et al. 2007. The effect of a 12-week combined exercise intervention program on physical performance and gait kinematics in community-dwelling elderly women. *J Physiol Anthropol*, 26:325–32.
- Cherrier MM, Craft S, Matsumoto AH. 2003. Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: a preliminary report. *J Androl*, 24:568–76.
- Choi DW, Koh JY, Peters S. 1988. Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. *J Neurosci*, 8:185–96.
- Chuang DM. 2004. Neuroprotective and neurotrophic actions of the mood stabilizer lithium: can it be used to treat neurodegenerative diseases? *Crit Rev Neurobiol*, 16(1–2):83–90.
- Clarke R, Smith AD, Jobst KA, et al. 1998. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch Neurol*, 55:1449–55.
- Coffey SM, Cook K, et al. (in press). Expanded clinical phenotype of women with the *FMR1* premutation. *Am J Med Genetics*.
- Cohen S, Masyn K, Adams J, et al. 2006. Molecular and imaging correlates of the fragile X-associated tremor/ataxia syndrome. *Neurology*, 67:1426–31.
- Cordivari C, Misra VP, Catania S, et al. 2004. New therapeutic indications for botulinum toxins. *Mov Disord*, 19(Suppl 8):S157–61.
- Cornish KM, Kogan C, Turk J, et al. 2005. The emerging fragile X premutation phenotype: Evidence from the domain of social cognition. *Brain Cogn*, 57:53–60.
- Cronister A, Schreiner R, Wittenberger M, et al. 1991. Heterozygous fragile X female: historical, physical, cognitive, and cytogenetic features. *Am J Med Genet*, 38(2–3):269–74.
- de Lau LM, Refsum H, Smith AD, et al. 2007. Plasma folate concentration and cognitive performance: Rotterdam Scan Study. *Am J Clin Nutr*, 86:728–34.
- Devdhar M, Ousman YH, Burman KD. 2007. Hypothyroidism. *Endocrinol Metab Clin North Am*, 36:595–615.
- Dombrowski C, Levesque ML, Morel ML, et al. 2002. Premutation and intermediate-size *FMR1* alleles in 10 572 males from the general population: loss of an AGG interruption is a late event in the generation of fragile X syndrome alleles. *Hum Mol Genet*, 11:371–8.
- Durga J, van Boxtel MP, Schouten EG, et al. 2007. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet*, 369(9557):208–16.
- Ebersbach G, Sojer M, Valldeoriola F, et al. 1999. Comparative analysis of gait in Parkinson's disease, cerebellar ataxia and subcortical arterio-sclerotic encephalopathy. *Brain*, 122(Pt 7):1349–59.
- Ellis T, de Goede CJ, Feldman RG, et al. 2005. Efficacy of a physical therapy program in patients with Parkinson's disease: a randomized controlled trial. *Arch Phys Med Rehabil*, 86:626–32.
- Farlow MR, Cummings JL. 2007. Effective pharmacologic management of Alzheimer's disease. *Am J Med*, 120:388–97.
- Farzin F, Perry H, Hessel D, et al. 2006. Autism spectrum disorders and attention-deficit/hyperactivity disorder in boys with the fragile X premutation. *J Dev Behav Pediatr*, 27(2 Suppl):S137–44.
- Field T, Diego M, Cullen C, et al. 2002. Fibromyalgia pain and substance P decrease and sleep improves after massage therapy. *J Clin Rheumatol*, 8:72–6.
- Franke P, Leboyer M, Gänssicke M, et al. 1998. Genotype-phenotype relationship in female carriers of the premutation and full mutation of *FMR1*. *Psychiatry Res*, 80:113–27.
- Franke P, Maier W, Hautzinger M, et al. 1996. Fragile-X carrier females: evidence for a distinct psychopathological phenotype? *Am J Med Genet*, 64:334–9.
- Gales BJ, Gales MA. 2007. Pyridostigmine in the treatment of orthostatic intolerance. *Ann Pharmacother*, 41:314–18.
- Galluccio L, Siddiqi N, Langenberg P, et al. 2002. Gender differences in burden and depression among informal caregivers of demented elders in the community. *Int J Geriatr Psychiatry*, 17:154–63.
- Gilron I, Watson CP, Cahill CM, et al. 2006. Neuropathic pain: a practical guide for the clinician. *CMAJ*, 175:265–75.
- Goldenberg DL, Burckhardt C, Crofford L, et al. 2004. Management of fibromyalgia syndrome. *JAMA*, 292:2388–95.
- Greco C, Hagerman RJ, Tassone F, et al. 2002. Neuronal intranuclear inclusions in a new cerebellar tremor/ataxia syndrome among fragile X carriers. *Brain*, 125:1760–71.
- Greco CM, Berman RF, Martin RM, et al. 2006. Neuropathology of fragile X-associated tremor/ataxia syndrome (FXTAS). *Brain*, 129(Pt 1):243–55.
- Greco CM, Soontarapornchai K, Wirojanan J, et al. 2007. Testicular and pituitary inclusion formation in fragile X associated tremor/ataxia syndrome. *J Urol*, 177:1434–7.
- Grigsby J, Brega AG, Jacquemont S, et al. 2006. Impairment in the cognitive functioning of men with fragile X-associated tremor/ataxia syndrome (FXTAS). *J Neurol Sci*, 248(1–2):227–33.
- Grigsby J, Brega AG, Leehey MA, et al. 2007. Impairment of executive cognitive functioning in males with fragile X-associated tremor/ataxia syndrome. *Mov Disord*, 22:645–50.

- Gunal DI, Afsar N, Bekiroglu N, et al. 2000. New alternative agents in essential tremor therapy: double-blind placebo-controlled study of alprazolam and acetazolamide. *Neurol Sci*, 21:315–17.
- Haan MN, Miller JW, Aiello AE, et al. 2007. Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. *Am J Clin Nutr*, 85:511–17.
- Hagerman PJ, Hagerman RJ. 2004. The fragile-X premutation: a maturing perspective. *Am J Hum Genet*, 74:805–16.
- Hagerman PJ, Hagerman RJ. 2004. Fragile X-associated tremor/ataxia syndrome (FXTAS). *Ment Retard Dev Disabil Res Rev*, 10:25–30.
- Hagerman RJ, Coffey SM, et al. 2007. Neuropathy as a presenting feature in fragile X-associated tremor/ataxia syndrome. *Am J Med Genet A*, 143:2256–60.
- Hagerman RJ, Hagerman PJ. 2002. The fragile X premutation: into the phenotypic fold. *Curr Opin Genet Dev*, 12:278–83.
- Hagerman RJ, Leehey M, Heinrichs W, et al. 2001. Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology*, 57:127–30.
- Hall DA, Berry-Kravis E, Hagerman RJ, et al. 2006. Symptomatic treatment in the fragile X-associated tremor/ataxia syndrome. *Mov Disord*, 21:1741–4.
- Harrigan EP, Miceli JJ, Anziano R, et al. 2004. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol*, 24:62–9.
- Hassin-Baer S, Korczyn AD, Giladi N. 2000. An open trial of amantadine and buspirone for cerebellar ataxia: a disappointment. *J Neural Transm*, 107:1187–9.
- Haverkamp R, Arean P, Hegel MT, et al. 2004. Problem-solving treatment for complicated depression in late life: a case study in primary care. *Perspect Psychiatr Care*, 40:45–52.
- Herrmann DN, Barbano RL, Hart-Goulean S, et al. 2005. An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy. *Pain Med*, 6:379–84.
- Hessl D, Glaser B, Dyer-Friedman J, et al. 2006. Social behavior and cortisol reactivity in children with fragile X syndrome. *J Child Psychol Psychiatry*, 47:602–10.
- Hessl D, Tassone F, Loesch DZ, et al. 2005. Abnormal elevation of FMR1 mRNA is associated with psychological symptoms in individuals with the fragile X premutation. *Am J Med Genet B Neuropsychiatr Genet*, 139:115–21.
- Ilg W, Golla H, Thier P, et al. 2007. Specific influences of cerebellar dysfunctions on gait. *Brain*, 130(Pt 3):786–98.
- Iwahashi CK, Yasui DH, An HJ, et al. 2006. Protein composition of the intranuclear inclusions of FXTAS. *Brain*, 129(Pt 1):256–71.
- Jacobs BL, Praag H, Gage FH. 2000. Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry*, 5:262–9.
- Jacquemont S, Farzin F, Hall D, et al. 2004. Aging in individuals with the FMR1 mutation. *Am J Ment Retard*, 109:154–64.
- Jacquemont S, Hagerman RJ, Hagerman PJ, et al. 2007. Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMR1. *Lancet Neurol*, 6:45–55.
- Jacquemont S, Hagerman RJ, Leehey M, et al. 2003. Fragile X premutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. *Am J Hum Genet*, 72:869–78.
- Jacquemont S, Hagerman RJ, Leehey M, et al. 2004. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. *JAMA*, 291:460–9.
- Jankovic J, Schwartz K, Clemence W, et al. 1996. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord*, 11:250–6.
- Jin P, Zarnescu DC, Ceman S, et al. 2004. Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway. *Nature Neuroscience*, 7:113–17.
- Koller WC, Royse VL. 1986. Efficacy of primidone in essential tremor. *Neurology*, 36:121–4.
- Leehey MA, Berry-Kravis E, Min SJ, et al. 2007. Progression of tremor and ataxia in male carriers of the FMR1 premutation. *Mov Disord*, 22:203–6.
- Leehey MA, Munhoz RP, Lang AE, et al. 2003. The fragile X premutation presenting as essential tremor. *Arch Neurol*, 60:117–21.
- Loesch DZ, Litewka L, Brotchie P, et al. 2005. Magnetic resonance imaging study in older fragile X premutation male carriers. *Ann Neurol*, 58:326–30.
- Louis E, Moskowitz C, Friez M, et al. 2006. Parkinsonism, dysautonomia, and intranuclear inclusions in a fragile X carrier: a clinical-pathological study. *Mov Disord*, 21:420–5.
- Luchsinger JA, Tang MX, Miller J, et al. 2007. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. *Arch Neurol*, 64:86–92.
- Mackin RS, Arean PA. 2005. Evidence-based psychotherapeutic interventions for geriatric depression. *Psychiatr Clin North Am*, 28:805–20, vii–viii.
- Mannerkorp K, Henriksson C. 2007. Non-pharmacological treatment of chronic widespread musculoskeletal pain. *Best Pract Res Clin Rheumatol*, 21:513–34.
- Miller JW, Green R, Mungas DM, et al. 2002. Homocysteine, vitamin B6, and vascular disease in AD patients. *Neurology*, 58:1471–5.
- Mischoulon D, Fava M. 2002. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am J Clin Nutr*, 76:1158S–61S.
- Miyai I, Fujimoto Y, Yamamoto H, et al. 2002. Long-term effect of body weight-supported treadmill training in Parkinson's disease: a randomized controlled trial. *Arch Phys Med Rehabil*, 83:1370–3.
- Morton SM, Bastian AJ. 2003. Relative contributions of balance and voluntary leg-coordination deficits to cerebellar gait ataxia. *J Neurophysiol*, 89:1844–56.
- Pesso R, Berkenstadt M, Cuckle H, et al. 2000. Screening for fragile X syndrome in women of reproductive age. *Prenat Diagn*, 20:611–14.
- Peters N, Kamm C, Asmus F, et al. 2006. Intrafamilial variability in fragile X-associated tremor/ataxia syndrome. *Mov Disord*, 21:98–102.
- Pohl M, Rockstroh G, Rückriem S, et al. 2003. Immediate effects of speed-dependent treadmill training on gait parameters in early Parkinson's disease. *Arch Phys Med Rehabil*, 84:1760–6.
- Protas EJ, Mitchell K, Williams A, et al. 2005. Gait and step training to reduce falls in Parkinson's disease. *Neuro Rehabilitation*, 20:183–90.
- Ramos MI, Allen LH, Mungas DM, et al. 2005. Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging. *Am J Clin Nutr*, 82:1346–52.
- Refsum H, Ueland PM, Nygård O, et al. 1998. Homocysteine and cardiovascular disease. *Annu Rev Med*, 49:31–62.
- Reisberg B, Doody R, Stöffler A, et al. Memantine Study Group. 2003. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*, 348:1333–41.
- Rolland Y, Pillard F, Klapouszczak A, et al. 2007. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. *J Am Geriatr Soc*, 55:158–65.
- Rousseau F, Rouillard P, Morel ML, et al. 1995. Prevalence of carriers of premutation-size alleles of the FMR1 gene – and implications for the population genetics of the fragile X syndrome. *Am J Hum Genet*, 57:1006–18.
- Sano M. 2003. Noncholinergic treatment options for Alzheimer's disease. *J Clin Psychiatry*, 64(Suppl 9):23–8.
- Santarelli L, Saxe M, Gross C, et al. 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*, 301(5634):805–9.
- Sapolsky RM. 2000. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry*, 57:925–35.
- Sasso E, Perucca E, Fava R, et al. 1991. Quantitative comparison of barbiturates in essential hand and head tremor. *Mov Disord*, 6:65–8.
- Scarmeas N, Albert M, Brandt J, et al. 2005. Motor signs predict poor outcomes in Alzheimer disease. *Neurology*, 64:1696–703.

- Selhub J, Miller JW. 1992. The pathogenesis of homocysteinemia: interruption of the coordinate regulation by S-adenosylmethionine of the remethylation and transsulfuration of homocysteine. *Am J Clin Nutr*, 55:131–8.
- Seshadri S, Beiser A, Selhub J, et al. 2002. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med*, 346:476–83.
- Sharpe PA, Williams HG, Granner ML, et al. 2007. A randomised study of the effects of massage therapy compared to guided relaxation on well-being and stress perception among older adults. *Complement Ther Med*, 15:157–63.
- Stanger O, Semmelrock HJ, Wonisch W, et al. 2002. Effects of folate treatment and homocysteine lowering on resistance vessel reactivity in atherosclerotic subjects. *J Pharmacol Exp Ther*, 303:158–62.
- Steffens DC, Snowden M, Fan MY, et al. 2006. Cognitive impairment and depression outcomes in the IMPACT study. *Am J Geriatr Psychiatry*, 14:401–9.
- Striano P, Coppola A, Vacca G, et al. 2006. Levetiracetam for cerebellar tremor in multiple sclerosis: an open-label pilot tolerability and efficacy study. *J Neurol*, 253:762–6.
- Sullivan AK, Marcus M, Epstein MP, et al. 2005. Association of FMR1 repeat size with ovarian dysfunction. *Hum Reprod*, 20:402–12.
- Svircev A, Craig LH, Juncos JL, et al. 2005. A pilot study examining the effects of neuromuscular therapy on patients with Parkinson's disease. *J Am Osteopath Assoc*, 105:26.
- Tandon R. 2002. Safety and tolerability: how do newer generation "atypical" antipsychotics compare? *Psychiatr Q*, 73(4):297–311.
- Tassone F, Adams J, Berry-Kravis EM, et al. 2007. CGG repeat length correlates with age of onset of motor signs of the fragile X-associated tremor/ataxia syndrome (FXTAS). *Am J Med Genet B Neuropsychiatr Genet*, 144:566–9.
- Tassone F, Hagerman RJ, Garcia-Arocena D, et al. 2004. Intranuclear inclusions in neural cells with premutation alleles in fragile X associated tremor/ataxia syndrome. *J Med Genet*, 41:e43.
- Tsao JC. 2007. Effectiveness of massage therapy for chronic, non-malignant pain: A review. *Evid Based Complement Alternat Med*, 4:165–79.
- Unutzer J, Katon W, Callahan CM, et al. IMPACT Investigators. Improving Mood-Promoting Access to Collaborative Treatment. 2002. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA*, 288:2836–45.
- Yu F, Kolanowski AM, Strumpf NE, et al. 2006. Improving cognition and function through exercise intervention in Alzheimer's disease. *J Nurs Scholarsh*, 38:358–65.
- Zesiewicz TA, Elble R, Louis ED, et al. Quality Standards Subcommittee of the American Academy of Neurology. 2005. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 64:2008–20.