Fragile X syndrome is a disease that does not get a lot of press. Most professionals have never heard of it. It effects more children than can be imagined. We feel that our fellow pharmacists must have at least an introductory recognition of this disease. For additional resources please contact the National Fragile X Foundation, PO Box 190488, San Francisco CA 94119, 1-800-688-8765. For your information, (from the Fragile X Foundation website), "Fragile X Syndrome is the most common known cause of inherited mental impairment." Our goal is to provide recognition of this disease to registered pharmacists. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

The program ID # for this lesson is 707-000-05-006-H01.

Pharmacists completing this lesson by June 30, 2008 may receive full credit.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. Define fragile X syndrome.
2. Describe the characteristics of fragile X syndrome.
3. Discuss a treatment regimen for fragile X based on specific symptoms.
4. Comment upon the genetic patterns associated with fragile X syndrome.
Introduction

As early as the 1890s, it was recognized that certain forms of mental retardation were more frequent among males than females, both in the general population and among those in prisons and other institutions. Initially this difference was thought to be due to the higher expectations placed on males at the time, and the fact that males were more likely to be in prison. However, later research noted that the IQ of the mother had a greater effect on the risk of mental retardation among sons than the IQ of the father. These and other observations led to the suggestion that a mutation in genes on the X chromosome might be the cause of this male predominance of mental retardation. The site of mutation of this gene on the X chromosome was eventually identified in the late 1970s and became known as the fragile X chromosome. The presence of mental retardation in association with the fragile X chromosome was originally called the Martin-Bell syndrome, after researchers who studied the disorder. Now called fragile X syndrome, it is considered one of the most common inherited causes of mental retardation, second only to Down’s Syndrome.

Fragile X syndrome results from a mutation in a single gene—the fragile X mental retardation (FMR1) gene—found in DNA on the X chromosome (location Xq27.3—the far end of the long arm of the X chromosome). This mutation is seen in the area of the gene responsible for initiating protein synthesis and results in the prevention of synthesis (or expression) of adequate amounts of fragile X protein. This lack of fragile X protein manifests in a variety of physical, behavioral, and cognitive deficiencies.

Function of fragile X protein

The function of the fragile X mental retardation protein (FMRP) has not been fully defined. It is known that the protein is widely distributed in both fetal and adult tissues, with high levels expressed in the brain and testes. Other areas where FMRP is normally expressed—such as the liver, lung, kidney, spinal cord, and gastrointestinal tract—are usually not affected in individuals with fragile X syndrome. It is thought that other proteins found in these tissues, namely FXR1 and FXR2, have a similar function as FMRP and compensate for the lack of FMRP. However, these other proteins do not replace the function of FMRP in the brain or testes in affected individuals, resulting in the symptoms of fragile X syndrome. FMRP is thought to be involved with RNA binding—either inhibition or stimulation of messenger RNA translation. This action is necessary for normal brain development. Neuroimaging studies of patients with fragile X syndrome have shown changes in brain size as well as reduced activation in some areas of the brain during cognitive tasks. Skeletal development is also affected by FMRP, as well as hypothalamic function.

The fragile X mutation

Normally, the FMR1 gene contains a base pair sequence of cytosine-guanine-guanine (CGG) that is repeated a specific number of times—somewhere between 6 and 40 repeated sequences. In individuals with fragile X syndrome, this sequence may be repeated hundreds of times, resulting in inactivation of the gene with little or no production of FMRP. This repeat of the CGG sequence is also referred to as a trinucleotide expansion. Inactivation of the gene is termed methylation, since the area of the gene responsible for promoting production of FRMP receives additional methyl groups not normally present, deactivating protein expression.

When the CGG sequence repeats or expands more than 200 times, it is considered a full mutation of the gene. A lesser number of repeats of the sequence (55 to 200), but more than normal, is called a premutation. Symptoms of fragile X are usually more severe in individuals with a full mutation of the gene compared to those with a premutation, since patients with a full mutation of the gene generally have no FMRP produced. Those with a premutation of the gene may have mild symptoms or no symptoms at all since there is still a certain amount of FMRP expressed. The amount of FMRP expressed is related to the number of CGG sequence repeats on the gene and the degree of methylation of the gene. Some patients, however, with a full mutation of the FMR1 gene show variability in the production of FMRP. This is termed as a “mosaic” pattern. With a mosaic pattern, individuals with fragile X will have cells that show as full mutation, as well as cells with a premutation.
Mosaicism is common among males with a fragile X mutation; 20% to 40% of males who have a full mutation of the fragile X gene will also have premutation present. This mix of full mutations and premutations results in a variable production of FMRP and differing degrees of impairment. Mosaicism is less common among females with gene mutations. The amount of FMRP production in fragile X is sometimes quantified using an “activation ratio”. Individuals with normal FMRP production have an activation ratio of 1; those with full mutation of the FMR1 gene (and no mosaicism) have an activation ratio of 0. Individuals with mosaicism or with premutation of the gene will have an activation ratio between 0 and 1. The activation ratio has been used in research to correlate the degree of behavioral or cognitive impairment and brain changes to the degree of reduction in FMRP expression.

Genetics of fragile X
Fragile X syndrome is an X-linked disorder and is inherited through the X chromosome. Since the disorder is X-linked, a male with a mutated gene cannot transmit fragile X syndrome to male offspring. However, the gene will be passed on to all female offspring. Females with the gene have a 50% chance of passing the gene on to any offspring, since they contribute one of their two X chromosomes. When the fragile X gene is passed from generation to generation, the risk of mental retardation and other features of fragile X syndrome increases. This is due to a phenomenon called anticipation—expansion of the number of CGG repeats as the gene is passed from mother to child. Each time the fragile X gene undergoes meiosis, the number of times the CGG sequence repeats within the gene is expanded. A gene with a premutation can be transformed in to a fully mutated gene, resulting in symptoms of fragile X syndrome or an increase in the severity of symptoms in the next generation. Therefore, a woman with no symptoms of fragile X syndrome, but with a premutation of the fragile X gene may give birth to an infant who exhibits signs and symptoms of the disorder. The severity of the disorder may increase over subsequent generations due to anticipation. Females with sons affected by fragile X syndrome are considered to be obligate carriers of the disorder.

Diagnosis of fragile X syndrome and genetic testing
The gene mutation that causes fragile X syndrome can be detected using DNA testing—either polymerase chain reaction (PCR) or a genomic Southern blot test. Southern blot testing is considered a more accurate method of testing for fragile X syndrome. It can be used to directly examine the fragile X gene and determine the number of CGG repeats and the degree of methylation. However, Southern blot testing is not easily used for widespread screening for the disorder. PCR testing is more suitable for testing a large number of samples, but is a less sensitive method for detecting full and premutations or mosaic patterns. It can identify the number of CGG repeats, but not the extent of gene methylation.

Routine testing during pregnancy for the presence of fragile X gene mutation is currently not done if there is not a family history of the disorder. The lack of a reliable method to accurately diagnose the disorder is one reason that routine screening during pregnancy is not recommended. Newborns are also not routinely screened for fragile X syndrome for the same reasons. Currently, there are no national standards for newborn screening and use of screening tests for newborns differs from state to state. In 1999, the American Academy of Pediatrics (AAP) Newborn Screening Task Force recommended the development of national newborn screening system standards and policies. The American College of Medical Genetics (ACMG) was given the task of outlining a method to standardize guidelines for state newborn screening programs. The ACMG report identified 29 disorders as primary targets for newborn screening. Fragile X syndrome was not included as a primary target for newborn screening. Although fragile X syndrome does meet one of the AMCG criteria for inclusion as a primary target for newborn screening—identification before clinical detection—testing is still not 100% reliable and there is no clear and effective treatment for the disorder.
Without screening for the presence of the fragile X gene, for many families, the diagnosis of fragile X syndrome is made after a long diagnostic process. Fragile X is generally not apparent at birth, and in most cases, delays or problems with normal development are not noticed until 9 to 13 months of age or later. For example, normal speech development (first use of words) usually begins by age 11 months. For a child with fragile X syndrome, first use of words can be delayed to 2 years of age. However, since the normal age range for word use can be as high as 18 months, there is a delay in identifying this problem with development in a child with fragile X syndrome. As a result, the diagnosis of fragile X syndrome is made at an average age of 30 to 35 months. And even if a problem with development is noted at an early age, genetic testing for fragile X is still often delayed and is more commonly done only after referral to a specialist, such as a neurologist, rather than pediatricians.

Factors affecting early diagnosis of fragile X syndrome:
- Not identifiable at birth.
- Lack of early, distinctive characteristics.
- Variability in phenotypic (genetic) expression.
- Lack of unique physical features.
- Failure of pediatricians to use developmental screening measures (as recommended by AAP) to detect delays and atypical behaviors.

The delay in diagnosis can have a number of consequences. For parents, a lack of confidence or trust in physicians can result, since in many cases physicians do not acknowledge atypical development in very young children despite concerns voiced by the parents. Unnecessary financial costs are incurred, resulting from repeated physician visits before a diagnosis is made. Delays in diagnosis also mean that early interventions for the child with fragile X are missed. And, finally, families may decide to have more children without being aware that a genetic disorder exists.

Although an important diagnostic tool, genetic testing should always be accompanied by formal genetic counseling. Trained genetic counselors are able to help parents and families understand the disorder, its genetics and risks of recurrence, as well as alleviate feelings of guilt and arrange for follow-up support. Most importantly, no harm should be done to the child or family as a result of genetic testing. Testing children for carrier status should only be done at an age when the individual can understand the disorder and the options for family planning.

Potential screening options for earlier identification of fragile syndrome:
- Screening of all women of child-bearing age.
  - Provides information regarding carrier status to allow for future decisions on reproduction.
  - Currently no public health policy on widespread screening program.
  - Would require increased public awareness of disorder.
- Screening of pregnant women.
  - Less expensive than screening all women of child-bearing age.
  - Limits reproductive decision-making options.
  - Requires greater public awareness of disorder.
  - May give parents more time for adjustment and preparation.
  - Would require expanded access to prenatal care.
- Newborn screening.
  - Screening programs are already established in all states.
  - Would allow for immediate enrollment into early intervention programs.
  - Allows for early management of associated medical problems.
  - Provides best opportunity to screen a large number of children.
  - Still provides information about carrier status of parents for future decisions

Clinical signs of fragile X syndrome
Fragile X syndrome can manifest with physical abnormalities as well as cognitive deficits and behavioral disorders. The severities of these characteristics differ by gender and the extent of gene mutation—a full mutation versus premutation. In general, males with fragile X syndrome tend to have more severe or pronounced symptoms of the disorder than females since females have two X chromosomes, only one of which has the FMR1 mutation. Individuals with a premutation present in the FMR1 gene may have no or only subtle features of fragile X syndrome. One particular syndrome associated with premutation in the FMR1 gene, fragile X-associated tremor/ataxia syndrome or FXTAS, has only been recently identified. FXTAS is a syndrome of progressive neurological symptoms seen among grandfathers of children with fragile X syndrome, with a prevalence
of about 20% to 30%. Loss of fine motor skills (writing, using eating utensils), problems with balance, and ataxia begin after age 50 and generally progress slowly with age until activities of daily living become difficult, often requiring assistance. FXTAS has only been associated with premutations of the gene and is not seen in individuals with a full mutation. Unlike fragile X syndrome, FXTAS only affects males who are carriers of the mutated gene. The only biochemical abnormality identified to date in males with FXTAS is an elevation in FMR1 messenger RNA. Females with premutation may experience premature ovarian failure, something that is also not seen among females with a full mutation of the gene.

**Physical characteristics of fragile X syndrome**

Physical signs of fragile X tend to manifest in childhood, differ by gender, and are variable; few characteristics are present in infants affected with the disorder. Not all males affected with fragile X syndrome show any physical characteristics of the disorder. Physical characteristics when present in males can include a long, narrow face; narrow inter-eye distance; enlarged ears, and a highly arched palate of the mouth. After puberty, macro-orchidism or enlarged testicular volume may also be present. Seizure disorders (usually complex partial seizures) are also common among males with fragile X syndrome, affecting about 15% to 20% of those with the syndrome. Other features may become more apparent in adulthood, such as hyperextensible joints and flat feet (possible due to an abnormality in connective tissue), strabismus (which may be present in infants), mitral valve prolapse, and serous otitis media. Many of these physical characteristics result from abnormalities in connective tissue growth. Females with fragile X syndrome may have no physical abnormalities; however, some of the facial features seen in males with fragile X syndrome may also be present in females.

**Cognitive deficits with fragile X syndrome**

Cognitive deficits are common with fragile X syndrome. Most males with the disorder are considered to be mentally impaired. In contrast, the cognitive skills of about half of females with fragile X syndrome are affected. The degree of mental impairment can range from mild to severe and is again related to the type of mutation present and the amount of FMRP expressed. Males with a full mutation of the gene have an average IQ of 41 (normal range IQ is generally considered to be 90-110 based on the Wechsler Adult Intelligence Scale). The average IQ of those with mosaicism is higher, about 60, because of higher FMRP production. It has been estimated that only about 13% of males affected with fragile X syndrome have IQs in the near normal to normal range. In addition, a decline in IQ is often seen after puberty—which may be less pronounced in females with the syndrome—suggesting a plateau or leveling-off in learning ability or potentially some type of progressive neurological dysfunction. About half of females with fragile X have normal or near-normal range IQs; however, certain types of cognitive problems may be present, such as problems with executive functioning (the ability to learn and interpret new information and make decisions based on that learning) and behavioral problems that may also affect learning, such as social interactions, disorganization, inattention, impulsivity, shyness, and moodiness.

Other specific cognitive impairments associated with fragile X syndrome include a delay in language development and repetitive speech (where words, phrases, or gestures are uncontrollably repeated, often described as echolalia or perseverative speech). The effect of fragile X syndrome on speech and language can be severe, with the extent of verbal expression frequently limited to three or four word sentences. Performance of visual-spatial tasks or numeracy (the ability to deal with numbers—count, add, subtract, multiple—mentally) and the processing of information are often affected to a greater extent than language.

**Behavioral problems with fragile X syndrome**

Because of the varied nature of fragile X syndrome, behaviors considered characteristic of the disorder may not be seen in every individual. Hyperactivity, attention problems, poor eye contact or gaze aversion, and repetitive or injurious behaviors (such as hand-flapping, body rocking, or hand-biting) are all associated with fragile X syndrome. Other behavioral problems, such as fluctuations in mood, social anxiety, shyness, and loss of temper, may be seen in early childhood, possibly as a response to increased sensitivity to the environment. Some of the behaviors seen in individuals with fragile X syndrome (such as repetitive speech or gestures) combined with overall developmental delays were thought to be associated with autism. However, studies have shown that, although some individuals with fragile X syndrome do have autism, the incidence of that disorder is no greater among individuals with fragile X syndrome than among those with other learning disabilities. Studies have also shown that males with fragile X syndrome have a greater understanding of language and conversation than males with autism. Relationships with family and close caretakers are generally characterized by strong, emotional attachment—something not in common with autism. However, more casual relationships—such as with classmates—are limited for those with fragile X syndrome.
Treatment of fragile X syndrome

Currently, no treatment is available for fragile X syndrome that would correct the FRMP deficiency. Therefore, any therapies are focused on improving the daily functioning of the individual and alleviating symptoms of the disorder.

Nonpharmacologic therapies

Nonpharmacologic therapies used in the treatment of fragile X syndrome need to focus specifically on behavioral or learning difficulties present in each individual, as well as problems with cognition and social interactions. Needed therapies will differ by age of the individual with fragile X. In infancy, gastroesophageal reflux may be a problem and interfere with normal feeding, requiring special care by the parents to prevent malnutrition in the infant. Occupational and physical therapy may be of benefit if joint instabilities, hypotonia, or motor delays are present. Otitis media or sinusitis can also affect a high percentage of infants with fragile X. Early therapy is important to avoid hearing loss.

Behavioral difficulties become more prominent in the toddler years and beyond, and delays in speech and social interactions are also more apparent. Calming techniques—using deep breathing, calming music or sounds—when environment or surrounding sensations are overwhelming to a very young child with fragile X syndrome can be of benefit. Speech, occupational, and language therapy become more essential as a fragile X child grows. Special classrooms which have an environment tailored to those with fragile X syndrome can also result in better learning and social behavior. Educators need to be aware of some of the cognitive problems associated with fragile X, such as gaze aversion and difficulties with information processing, numeracy, and performance of visual-spatial tasks. Behavioral problems—including aggressive behavior and attention deficit and hyperactivity—increase with age and require continued therapy. Physical problems also become more apparent in the school-age child with fragile X, due to connective tissue dysplasia and may include scoliosis, flat feet, hernias, cardiac murmur, and mitral valve prolapse; enuresis is also common. Problems encountered by individuals with fragile X in adulthood are extensions of those seen during childhood and adolescence. Therefore, teaching in the areas of daily living skills and vocational training should be started during the teenage years to allow the individual with fragile X a certain degree of independent living as an adult. Emotional issues that emerge in young adulthood, such as sexuality and anxiety about separation from family, also need to be addressed.

Pharmacologic therapies

As with nonpharmacologic therapies, use of pharmacologic agents need to be focused on specific problems manifesting with fragile X syndrome, with the goal of maximizing daily functioning while minimizing adverse events associated with drug therapy. For many individuals with fragile X syndrome, more than one medication is needed. Behavioral problems in fragile X occur at a rate that is higher than would be expected based on an individual’s cognitive abilities. Attention deficit/hyperactivity disorder-like symptoms, anxiety-related symptoms, emotional liability, and aggressive or self-aggressive behaviors are the major targets of medication use. Drug therapies appear to be more common among younger individuals (children and adolescents) with fragile X syndrome and in males with the disorder. Although pharmacologic therapy has been found to be effective in practice, there are few clinical trials available to provide a guide to treatment. Therefore, selection of medications is based on target symptoms.

Stimulant medications—methylphenidate and amphetamines—may be the most frequently used agents among children and adolescents with fragile X syndrome. The overall response rate to the use of stimulants has been reported to be about 75% for symptoms of hyperactivity and attention deficit in children and adolescents. Better attention, lower motor activity, and better academic performance have been associated with the use of stimulants. However, some symptoms of fragile X may be worsened with stimulants, such as anxiety and aggression. The IQ of an individual may affect the efficacy of stimulants—overall, individuals with a higher IQ respond better to stimulants, whereas a lower IQ is associated with more adverse events.

The α2-adrenergic agonists (clonidine and guanfacine), although less commonly used, have been reported to be about 70% to 80% effective in controlling hyperactive, impulsive, or aggressive behavior. These agents are considered by some to be the drugs of choice, alone or in combination with stimulants and serotonin-agonists, for treatment of hypersensitivity or hyperarousal to sensory stimuli. In addition, the α2-adrenergic agonists may be especially useful in young children (less than 5 to 6 years of age) who do not respond to or cannot tolerate stimulants, or for those individuals with sleep disturbances.

Antidepressants—primarily the selective serotonin reuptake inhibitors—have been reported to be used in about 50% of individuals with fragile X. These agents are successful in the treatment of anxiety, depression, compulsion, mood liability, and aggression, with response rates of 50% to 60% reported. Beta-adrenergic antagonists (propranolol, pindolol, and nadolol) are also effective agents for anxiety, hypersensitivity or hyperarousal, and aggressive behaviors. Response rates as high as 80% have been reported among individuals with self-injurious or aggressive behavior.

Seizures disorders can occur in up to 20% of individuals with fragile X syndrome and are controlled with anticonvulsants. In addition, some anticonvulsants are effective as mood stabilizers for individuals with bipolar or mood disorders. Psychiatric...
disorders or extreme behaviors are also treated with antipsychotic agents. However, the use of antipsychotics is generally low in the fragile X population, in part due to the side effect profiles of these agents, such as weight gain, sedation, and extrapyramidal reactions. The use of antipsychotics, in general, should be reserved for cases where aggressive behavior becomes dangerous and requires immediate control.

Folic acid has also been used, with first reports of its beneficial use published in 1982. Folic acid has been shown to be involved with neurotransmission, brain development, and dopamine and serotonin distribution and metabolism, and is found concentrated in the synaptic regions of central nervous system neurons. Clinical trials have shown mixed results with some reporting improvement in behavior and development in males with fragile X syndrome, resulting in improvements in cognition. Families have also reported a decrease in hyperactivity and improvements in attention span in children with fragile X syndrome with the use of folic acid. documentation of the effectiveness of folic acid is difficult, however, since many parents continue to use the agent if they perceive any improvement in a child’s behavior, language, cognition, or motor skills. Folic acid is generally well tolerated, although diarrhea has been reported. In addition, it is unclear if folic acid will exacerbate pre-existing seizure disorders; therefore, its use is not recommended in patients with uncontrolled seizures.

**Pharmacologic therapies for fragile X syndrome**

**Anticonvulsants and mood stabilizers**
- Carbamazepine
- Valproic acid
- Lithium
- Gabapentin
- Lamotrigine
- Topiramate
- Phenobarbital
- Phenytion

**Stimulants**
- Methylphenidate
- Dextroamphetamine

**Antidepressants**
- Venlafaxine
- Nefazodone
- Bupropion
- Imipramine
- Desipramine
- Fluoxetine
- Sertraline

**Miscellaneous agents**
- Amantadine
- Buspirone
- Clonidine
- Guanfacine
- Folic acid

**Antipsychotics**
- Risperidone
- Olanzapine

**Beta-adrenergic receptor antagonists**
- Propranolol
- Nadolol
- Pindolol

**alpha-2 adrenergic agonists**
- Clonidine
- Guanfacine

**Summary**

Fragile X syndrome is one of the most common genetic causes of mental retardation, and results from a mutation of the X-linked fragile X gene. Severity and type of symptoms of fragile X syndrome vary and are related to the amount of FMRP protein produced. Cognition, behavior, and physical development can all be affected with fragile X syndrome. The disorder is generally less severe among females, since one X chromosome is unaffected. As with any other inherited developmental disorder, early identification and early intervention is important to improve the quality of life in those with fragile X. However, diagnosis of fragile X is often delayed, since symptoms are not apparent at birth. Genetic testing is one method to identify children with fragile X and should be considered if there is a family history of the disorder or if normal development in a child is delayed. No specific course of treatment is available for fragile X syndrome. Therapies generally consist of behavioral interventions, special education programs, pharmacologic treatment, and physical therapy.

**References**

Quiz—Please select the most correct answer

1. Fragile X can best be described as:
   A. An X-linked inherited form of mental retardation
   B. A relatively rare syndrome that affects males & females to the same degree
   C. An easily diagnosed condition with clear & effective treatments
   D. None of these

2. Screening for Fragile X is currently included in mandatory newborn testing.
   A. True
   B. False

3. A CGG sequence repeat of 55 to 200 in the FMR1 gene is considered:
   A. Normal
   B. A full mutation of the FMR1 gene
   C. A premutation of the FMR1 gene
   D. A mosaic pattern of mutation

4. Southern blot testing can determine both the number of CGG expansions & the degree of methylation in the FMR1 gene.
   A. True
   B. False

5. Individuals with FMR1 genes showing cells with full mutation as well as cells with a premutation are considered to:
   A. Be normal with regards to FMR1 gene
   B. Have severe manifestation of fragile X syndrome
   C. Have mosaic pattern of mutation, with variable production of fragile X protein & different degrees of impairment
   D. None of these

6. A female with a mutated gene has a 50% chance of transmitting fragile X syndrome to any offspring.
   A. True
   B. False

7. Physical characteristics of fragile X syndrome can include:
   A. Facial changes, such as enlarged ears & a long, narrow face
   B. Hyperextensible joints
   C. Seizure disorders
   D. All of these

8. In comparison to males, females with fragile X syndrome may have:
   A. Few or no physical characteristics of the disease
   B. Better cognition & a higher IQ
   C. Generally less severe deficiencies because of 2nd X chromosome
   D. All of these

9. Treatment of fragile X can include:
   A. Speech & language therapy
   B. Occupational & physical therapy
   C. Educational interventions
   D. All of these

10. Which statement is true?
    A. Folic acid is an established pharmacologic therapy for fragile X
    B. Folic acid has been shown to mimic the actions of FMRP, replacing the deficient protein
    C. Folic acid has been shown to be effective in improving behavior & development in some males
    D. All of these
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