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Levetiracetam in pregnancy

Epilepsy in children and treatment

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Levetiracetam in pregnancy

(Results from the UK and Ireland epilepsy and pregnancy registers)

Prenatal exposure to antiepileptic drugs (AEDs) increases the risk of major congenital malformations (MCM) from the background risk of 1% to 2% to between 4% and 9%. Over the last 10–15 years, reports from several epilepsy pregnancy registers have confirmed the teratogenic potential of certain AEDs, in particular valproate. The result has been a prescribing shift toward lamotrigine and more recently levetiracetam for women with epilepsy (WWE) of childbearing age. This has particularly been the case for those with idiopathic generalized epilepsy syndromes, for whom valproate would usually have been considered the AED of choice. In 2006, the UK Epilepsy and Pregnancy Register published reassuring, if preliminary, results on the risks for MCM with levetiracetam use in pregnancy, with no MCM being observed in 39 pregnancies exposed to levetiracetam monotherapy, and only 3 MCM in 78 pregnancies exposed to levetiracetam taken as part of a polytherapy regimen. More recently, the North American AED Pregnancy Registry reported similarly reassuring results, with only 11 MCM in 450 levetiracetam monotherapy exposures (total MCM rate 2.4%). In contrast, the UCB AED Pregnancy Registry reported 12 MCM among 253 levetiracetam monotherapy exposures (MCM rate 4.7%) and 13 MCM in 105 polytherapy exposures (MCM rate 12.4%). Neither the UK Epilepsy and Pregnancy Register nor the North American AED Pregnancy Registry studies replicated results from previous animal and a preliminary human study which had suggested an increase in skeletal abnormalities and low birth weight, respectively. In the UCB registry, 3 of the 10 MCM occurring in children exposed to levetiracetam in the first trimester were skeletal abnormalities.

In contrast to how the effects of AEDs on the developing fetus have previously been reported, the effect of levetiracetam on neurodevelopment has been presented before the risk for MCM has been reported in meaningful numbers of pregnancies. In the joint study by the Liverpool and Manchester Neurodevelopment Group and the UK Epilepsy and Pregnancy Register, only 8% of children exposed to levetiracetam in utero compared to 40% of children exposed to valproate in utero had below average scores for development. The children exposed to levetiracetam in utero had similar developmental scores to the control group, and when compared to valproate, levetiracetam exposure was associated with higher overall developmental quotient scores.

In this article, we present results from the UK and Ireland Epilepsy and Pregnancy Registers in 671 pregnancies exposed to levetiracetam in the first trimester between October 2000 and August 2011.

METHODS The UK Epilepsy and Pregnancy Register is a prospective, observational registration and follow-up study that was set up in 1996 to determine the relative safety of all AEDs taken in pregnancy. The Irish Epilepsy and Pregnancy Register was set up in 2001 and joined the UK Epilepsy and Pregnancy Register in 2007. The 2 studies have the same methodology; both have been approved by national and regional ethical committees and obtain written informed consent from participants. Full details have been published previously. Suitable cases were defined as women with epilepsy who became pregnant while taking levetiracetam, either in monotherapy or polytherapy and who were referred before the outcome of the pregnancy was known. Most participants register during the first trimester, but registrations are accepted at any time before delivery, as long as the outcome has not been believed to be determined based on the result of any formof prenatal testing. Cases that are referred following antenatal diagnosis of a probable or definite MCM are excluded.

The UK Epilepsy and Pregnancy Register records AED name and dosage at registration only in the majority of cases. If we are informed of dose changes, either during the pregnancy or at the time of follow-up, then the dose recorded is the highest known dose taken during pregnancy. If a second AED is added at any point during the pregnancy, this is recorded as a polytherapy exposure.

Recording of smoking and alcohol use, serum AED levels and analysis of individual physicians' clinical practice (therapeutic drug monitoring or clinical assessment) is not part of the methodology of this study and are not available for this analysis.

An MCM was defined as an abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered in the first 6 weeks of life, according to the definitions and lists of disorders in the EUROCAT registry.

Statistical analysis. Malformation rates were calculated as [total number of live births with a malformation] + [total number of pregnancy losses with a malformation] ÷ [total number of live births] + [total number of pregnancy losses with a malformation]. Ninety-five percent confidence intervals (CIs) were calculated using the traditional method. Fisher exact test, x^2 test, analysis of variance and relative risks were used to compare characteristics between groups.

RESULTS Through August 2011, complete outcome data were available for 671 pregnancies. Of these, 304 had been exposed to levetiracetam in monotherapy and 367 had been exposed to levetiracetam in combination with at least one other AED. Pregnancy outcome details for all exposures are shown in table 1. Two of those on polytherapy combinations had previously had children with MCM (patients 9 and 18). Of all pregnancies exposed to levetiracetam, 93.3% resulted in a live birth and 21 had an MCM (total MCM rate 3.3% [95% CI 2.2%–5.1%]).

For monotherapy exposures, there was no significant relationship between mean birth-weight or mean gestational age and levetiracetam dose, even when outcomes were compared for those taking doses of less than 1,000 mg daily and those taking 3,000 mg daily or more ($p = 0.43$ for mean birthweight; $p = 0.11$ for gestational age). The mean levetiracetam dose in pregnancies ending in stillbirths was slightly higher than in those resulting in live births or spontaneous abortions (2,250 mg compared to 1,660 mg and 1,733 mg, respectively). This was not statistically significant ($p = 0.22$). The mean levetiracetam dose for those with MCM was 3,000 mg daily, compared to 1,148 mg for those with minor malformations and 1,680 mg for those with normal pregnancy outcomes ($p = 0.09$). There was no correlation between MCM occurrence and preconceptual folic acid intake (50% in those with MCM compared to 61% in those without, $p = 1.00$).

Information on levetiracetam dose was not available for one woman who had a child with a MCM on levetiracetam polytherapy. This individual was excluded from any analyses regarding dose. Two other women in the polytherapy group who had children with MCM were only taking 250 mg daily of levetiracetam.

For polytherapy exposures, there was no obvious relationship between seizure control and the risk of MCM, with 29.6% of women with normal outcomes compared to 10.5% of those with children with MCM having generalized tonic-clonic seizures in the first trimester (p = 0.11). Polytherapy exposures ending in spontaneous abortions were exposed to higher mean levetiracetam doses than those ending in live births or stillbirths (2,306 mg compared to 1,801 mg and 1,000 mg respectively).

Table 1 Cumulative outcomes for pregnancies exposed to levetiracetam

	Levetiracetam monotherapy exposures	Levetiracetam as part of a polytherapy regimen
No. of exposures	304	367
Outcome		
Live birth	286	340
Spontaneous abortion	15	22
Stillbirth	2	2
Induced abortion	1	3
Mean dose levetiracetam, mg (range)	1,670 (250–5,000)	1,827 (100–5,000)
Mean gestational age at delivery, wk	38.3	37.0
Mean birth-weight, g (range)	3,328 (1,049–4,615)	3,202 (785–4,730)
Sex		
Male	136	162
Female	136	164
Unknown	32	41
Mode of delivery		
Vaginal	152	156
Cesarean	73	126
Forceps	25	22
Ventouse	31	30
Unknown	23	33
Seizures in pregnancy, n (%)		
Tonic-clonic ± other	54 (17.8)	106 (28.9)
Other only	62 (20.4)	97 (26.4)
None	172 (56.6)	132 (36.0)
Not recorded	16 (5.2)	32 (8.7)
Preconceptual folic acid		
No	108	160
Unknown	22	31
Yes	174	176
Major malformations	2	19
Major congenital malformation rate (95% confidence interval)	0.70 (0.19–2.51)	6.47 (4.31–9.60)
Minor malformations	13	22
All malformation rate (95% confidence interval)	5.24 (3.20–8.47)	11.99 (8.96–15.86)

This was statistically significant (p = 0.02). For polytherapy exposures, there was no correlation between levetiracetam dose and presence of MCM (p = 0.91). The mean dose of levetiracetam in those with MCM was 1,819 mg compared to 1,784 mg in those with minor malformations and 1,830 mg in those with normal pregnancy outcomes. The MCM rate varied according to the AED given in combination with levetiracetam. The MCM rate for lamotrigine and levetiracetam combinations was 1.8% (95% CI 0.5 – 6.2), compared to 6.9% (95% CI 1.9 – 22.0, relative risk 1.41) in those exposed to valproate and levetiracetam and 9.4% (95% CI 4.4 – 19.0, relative risk 1.91) for carbamazepine and levetiracetam combinations. No MCM were observed in 20 live births to women taking topiramate and levetiracetam polytherapy. For polytherapy exposures, there was no correlation between the occurrence of MCM and preconceptual folic acid intake (55% in those with MCM compared to 52.2% in those without, p = 0.81).

DISCUSSION This study confirms previous reports of the low MCM rate with levetiracetam monotherapy exposure during pregnancy. At 0.7% this is lower than previously reported by the North American AED Pregnancy Registry (2.4%) and the UCB Antiepileptic Drug Pregnancy Registry (4.7%) and is similar to MCM rates observed in the nonepilepsy population.

No clear effect of levetiracetam dose on MCM rate was observed in monotherapy or polytherapy exposures. While in the monotherapy group the mean total daily dose of levetiracetam in those resulting in an MCM was nearly double that for those without an MCM, due to the numbers available for study, the results were not statistically significant. In keeping with our previous results we did not find there to be any reduction in mean birth weight for levetiracetam-exposed pregnancies, even at doses over 3,000 mg daily.

MCM rates in those exposed to levetiracetam as part of a polytherapy regimen were significantly higher than for those exposed to levetiracetam in monotherapy. This is in line with previous studies that have consistently shown higher MCM rates for polytherapy compared with monotherapy regimens, both overall and for individual AED regimens. While there are likely a number of reasons for the higher MCM rate in pregnancies exposed to polytherapy regimens, we found the total daily dose of levetiracetam to be similar for the 2 groups. Seizure control was worse in those exposed to levetiracetam as part of a polytherapy regimen and may be implicated in the higher MCM rate for polytherapy exposures.

In keeping with previous studies, we found different risks from different drug combinations that included levetiracetam. While exposure to levetiracetam in combination with valproate or carbamazepine appeared to carry a higher risk for MCM when compared to combinations containing levetiracetam and lamotrigine, due to the small numbers involved, the results did not reach statistical significance. While larger studies are required, the increased risk with polytherapy exposures containing valproate was in keeping with observations from other studies, including the North American AED Pregnancy Registry and the International Lamotrigine Pregnancy Registry. The increased MCM rate for levetiracetam and carbamazepine in combination was unexpected and requires replication in other studies.

Dose was an important predictor of outcome in the group exposed to levetiracetam as part of a polytherapy regimen, with pregnancies ending in spontaneous abortions being exposed to significantly higher mean daily doses of levetiracetam. Those pregnancies ending in spontaneous abortion were more likely to be in patients on 3 or 4 AEDs (29.2% on 3 drugs and 16.6% on 4 drugs) compared to those resulting in live births or stillbirths (19.2% on 3 drugs and 2.9% on 4 drugs). These patients were also on higher mean total daily doses of other AEDs; for example, for lamotrigine, 500mg compared to 408 mg, and for topiramate, 800 mg compared to 361 mg, respectively. A similar trend was not seen in the monotherapy group and it is felt that these findings more likely reflect the higher mean drug load in the spontaneous abortion group rather than higher levetiracetam doses.

Source : *Ellen Mawhinney, MB, John Craig, MB, Jim Morrow, PhD, Aline Russell, MB, W. Henry Smithson, MD, Linda Parsons, MD, Patrick J. Morrison, MD, Brenda Liggan, MSc, Beth Irwin, Norman Delanty, FRCPI, Stephen J. Hunt, MB, Levetiracetam in pregnancy, Neurology 2013;80:400–405.*

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When To Treat Seizures

Seizures are treated if they recur or appear likely to recur. Not all children will require treatment for seizures, especially if the child only has one seizure and the EEG and MRI (or other imaging test) are normal.

Even when treatment is necessary, the long-term impact of seizures is small for most children, especially if there are no underlying abnormalities in the brain.

General Information About Medications

Medications used to prevent seizure are called antiepileptic drugs (AEDs).

- Most medications are started at a low dose and slowly increased until seizures no longer occur.
- The dose of the medication may be adjusted as the child grows and weight increases or as new medications are added for other problems (eg, asthma).
- A second AED may be added or substituted if the first drug was only partially effective in stopping seizures, or if there were significant side effects with the first drug.

Interactions with other medications - Many AEDs can interact with other medications; parents should be sure that their child's healthcare providers and pharmacist are aware of all prescription and nonprescription medications taken by the child.

Monitoring during treatment - Occasional blood testing is recommended with some drugs to monitor the level of the drug in the body. Testing may be done on a regular basis and when the dose changes.

Allergic reaction - All drugs have the potential to cause an allergic reaction. The first sign of a drug allergy is often a rash; parents who notice this should call their healthcare provider immediately. Rashes can be caused by many different things, including some common viruses, and the provider will evaluate the situation to decide whether or not the rash is related to the AED. Do not stop giving the antiepileptic medication unless the child's doctor says so because some medications should not be stopped suddenly.

Risk of suicide - An expert review suggested that antiepileptic drugs can slightly increase the risk of suicidal thoughts in children over the age of five. In considering whether or not to use AEDs to treat seizures, the parent(s) and physician must balance the small increased risk of suicidal thoughts against the risk of continued seizures if the child is not adequately treated. Any mention of suicidal thoughts or feelings should be taken seriously and reported to the child's physician.

Dealing with side effects - AEDs often have side effects, some of which can be bothersome and interfere with a child's ability to function (table 1). Side effects can sometimes be managed by lowering the medication's dose or changing the dosing schedule.

Anti-seizure medications

Drug name	Side effects*
Carbamazepine (Tegretol®, Carbatrol®)	Diarrhea, rash, serious allergic reaction, low blood sodium levels
Ethosuximide (Zarontin®)	Trouble sleeping, hyperactivity
Lacosamide (Vimpat®)	Heart rhythm changes
Rufinamide (Banzel®)	Heart rhythm changes
Gabapentin (Neurontin®)	Weight gain
Lamotrigine (Lamictal®)	Rash, with risk of a serious allergic reaction
Levtiracetam (Keppra®)	Aggressive behavior, irritability
Oxcarbazepine (Trileptal®)	Rash, serious allergic (Trileptal®) reaction, low blood sodium levels
Phenobarbital (Luminal®)	Slowed thinking, rash, hyperactivity and other behavioral changes in children
Phenytoin (Dilantin®, Phenytek®)	Abnormal growth of the gums, increased body hair, rash, swollen lymph nodes (glands)
Pregabalin (Lyrica®)	Weight gain
Tiagabine (Gabitril®)	Tremor, difficulty concentrating, abdominal pain
Topiramate (Topamax®)	Weight loss, numbness and tingling in the hands difficulty thinking and feet; clearly
Valproic acid (Depakote®, Depakene®)	Weight gain, hair loss, bruising, sprinkled on food) tremor, liver toxicity
Zonisamide (Zonegran®)	Weight loss, difficulty thinking clearly

Many of these medications can also cause sedation and/or fatigue, dizziness, double vision and nausea.

* These side effects occur in some, not most patients.

Parents should not assume that a side effect is caused by medication; it is possible that the child's seizure disorder or another condition is responsible. Parents should discuss any concerns about side effects with their child's healthcare provider, and should never stop their child's AED without first discussing it with their child's provider.

Stopping antiepileptic drugs - Most children who are treated with AEDs continue taking them until there have been no seizures for two years. After two years of being seizure-free, the chance of having another seizure is reduced to 30 to 40 percent. This is true for all types of seizures, although children with other neurologic problems (eg, cerebral palsy) have a slightly higher risk of having another seizure after the AED is stopped.

AEDs should be tapered slowly rather than stopped suddenly. This may mean that the dose is reduced on a weekly basis over several months. Parents should discuss the tapering schedule with the child's healthcare provider.

Specific antiepileptic drugs - There are a number of anti-seizure medications available. A table that briefly describes these medications is available here.

Other Treatments

Dietary treatment - A special diet, known as the ketogenic diet, has been used as a treatment for children with some types of seizures that do not respond to AEDs. The diet consists of high fat, relatively low carbohydrate and adequate protein. The diet does not usually "cure" the seizures, but it lowers the likelihood of seizures by at least 50 percent in approximately 40 percent of patients, particularly those between one and 10 years of age.

Parents should not attempt to start their child on a ketogenic diet on their own; it should be supervised by a well-trained dietitian in an Epilepsy Center with experience managing the diet. The diet is usually started in a hospital setting, although some experts are able to manage patients at home. The child must be closely monitored to ensure he or she is growing and getting all the necessary nutrients. The diet is often continued for at least two years in children who improve significantly.

The restriction on eating carbohydrates may be difficult for some children, especially those who are reluctant to try new foods. Parents, teachers, relatives, and friends need to understand that even one bite or taste of a restricted food can lead to a seizure. The diet may significantly change experiences like birthday parties and holidays, which frequently include high carbohydrate foods. Talking to other parents of children who have used the diet may be helpful in deciding whether to attempt it.

Vagus nerve stimulation (VNS) - The vagus nerves are a pair of large nerves located in the neck. Stimulating the left vagus nerve intermittently with electrical pulses can reduce the frequency of seizures in some people. This requires surgically implanting a small device or pacemaker, called a stimulator, under the skin in the left upper chest, which is attached to a wire secured around the nerve in the neck.

Often, many months of VNS are needed before benefit is seen. Studies show that VNS reduces seizure frequency by about 50 percent in 30 to 40 percent of individuals. VNS is approved for children over age 12 years, although it has been used in younger children. Some patients are able to significantly shorten or abort seizures by use of the VNS magnet at the onset of a seizure.

Brain surgery - Children whose seizures do not respond to medications may be candidates for brain surgery. Surgical treatments may be considered for children who have persistent, frequent seizures that are not controlled after a trial of at least two to three AEDs.

Most epilepsy surgeries involve removal of the area of the brain causing the seizures. This area may be as small as the tip of a finger (focal cortical resection or topectomy) or as large as an entire lobe of the brain (lobectomy) or even the entire half of the brain (hemispherectomy).

The area causing seizures is often found to be a scar (gliosis), an area of abnormal brain growth (dysplasias or hamartomas), or rarely, a tumor (neoplasias). Many of these abnormalities can be seen on MRI scans, but not all. Some children will require other specialized tests in order to localize the exact spot where the seizures are arising. The risk and benefits of epilepsy surgery must be discussed in detail with an epilepsy team, including a neurosurgeon and/or neurologist prior to proceeding.

Care During Seizures

If you witness your child's seizure, it is important to prevent the child from harming him or herself.

- Place the child on their side to keep the throat clear and allow secretions (saliva or vomit) to drain. Do not try to stop the child's movements or convulsions. Do not put anything in the child's mouth, and do not try to hold the tongue. It is not possible to swallow the tongue, although some children may bite their tongue during a seizure, which can cause bleeding. If this happens, it usually does not cause serious harm.
- Keep an eye on a clock or watch. Seizures that last for more than five minutes require immediate treatment.
- Move the child away from potential hazards, such as a stove, furniture, stairs or traffic.
- Stay with the child until the seizure ends. Allow the child to sleep after the seizure if he/she is tired. Explain what happened and reassure the child that they are safe when they awaken.
- Discuss a post-seizure plan of care with your child's health-care provider to determine if and when to call the doctor or go to the emergency room and when to give additional anti-seizure medicine after a seizure.

When to call for help - Call for an ambulance in the following situations:

- If the seizure lasts for more than five minutes, one person should stay with the child while another person calls for emergency medical assistance, available by dialing 911 in the United States and Canada.

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- If the child is seriously injured during the seizure (eg, falls and hits head)
- If the child is having difficulty breathing and/or the skin is blue after the seizure
- If another seizure occurs immediately or if the child cannot be aroused after the seizure

Status epilepticus - Status epilepticus is the name for a prolonged seizure (greater than 10 minutes) or clusters of seizures in which the child does not awaken between seizures. Status epilepticus requires emergency medical attention to stop seizures and prevent them from recurring. You should not attempt to drive a child with status epilepticus to the hospital; an ambulance should be called.

If your child has a history of status epilepticus, you should develop a plan for future episodes with your child's healthcare provider; this may include having emergency treatment available at home. Home treatment usually involves giving one dose of diazepam gel into the rectum if a child's seizure lasts more than five minutes.

Living With Seizures

Children with epilepsy often need to make lifestyle changes to minimize the frequency of seizures and possible dangers associated with seizures. However, you must balance your concerns about your child's health so that the child can have as full and independent a life as possible.

Reducing and avoiding harm - There are many things that parents of a child with epilepsy need to know about decreasing the risk of harm due to seizures and seizure treatment. A few tips are listed here.

- Parents should teach their child to avoid biking, skating, and skateboarding on streets with heavy traffic. All children need to wear protective gear, including a helmet, during these activities.
- Activities at heights (eg, climbing a tree or rope) should be avoided to prevent serious falls if the child has a seizure while climbing.
- Always supervise the child around water, including bathtubs, at the beach, and near wading pools. Showers may be unsupervised, but swimming should be closely supervised at all times by someone who is aware of their condition. If seizures are poorly controlled, a life jacket should be worn when they are in the water.
- Parents should talk to their child's teachers and other parents about their child's condition and what to do in case a seizure occurs.
- Children with epilepsy should wear a medical identification bracelet or necklace at all times. If a seizure occurs and the child is unable to explain their condition, this will help responders give the proper care as quickly as possible. The identification device should include the child's condition, a list of known allergies, as well as the name and phone number of an emergency contact. One device, Medic Alert, provides a toll-free number that emergency medical workers can call to find out a person's medical history, list of medications, family emergency contact numbers, and healthcare provider names and numbers.
- Encourage the child to sleep well and take medications on time.
- Driving restrictions for people with seizures vary from state to state and country to country. Some people with seizures are not allowed to drive at all, while others can drive with restrictions (eg, unless a seizure has occurred recently or medication type or dose is changing).
- Teens with epilepsy need counseling about the effects of seizures and seizure medications on sexual activity. All medications have the potential to cause birth defects if taken during pregnancy, although some may be riskier than others. Also, birth control pills may not be effective in preventing pregnancy when used with some AEDs.
- Parents of teens should also discuss the increased risk of seizures due to drinking alcohol or using recreational drugs. Alcohol and drugs (prescription, over-the-counter and recreational) can interact with AEDs, making them less effective and increasing the risk of seizure. Also, the effects of alcohol and the side effects of AEDs can be enhanced when combined.

School and seizures - Children with epilepsy are often fearful of having a seizure while at school. Seizures can be an embarrassing and frightening event, but advance planning can help a child to feel more confident. Parents should be sure that their child's teacher, school nurse and other faculty are aware of the child's condition, need for treatment, and what to do in case the child has a seizure. Local epilepsy groups often have information that parents can give to school personnel that describes what epilepsy is and how it is treated. Meeting to discuss an individual child's needs is often helpful.

Children with epilepsy sometimes have difficulty keeping up academically with peers as a result of missing school for appointments or tests. While intelligence is not usually affected by epilepsy, seizures and the side effects of anti-seizure medications can affect a child's ability to perform well on tests and remember detailed information. The child's neurologist or other healthcare provider can be helpful in providing guidance to parents and children about difficulties with school performance.

Source : *http://www.uptodate.com/contents/treatment-of-seizures-in-children-beyond-the-basics*

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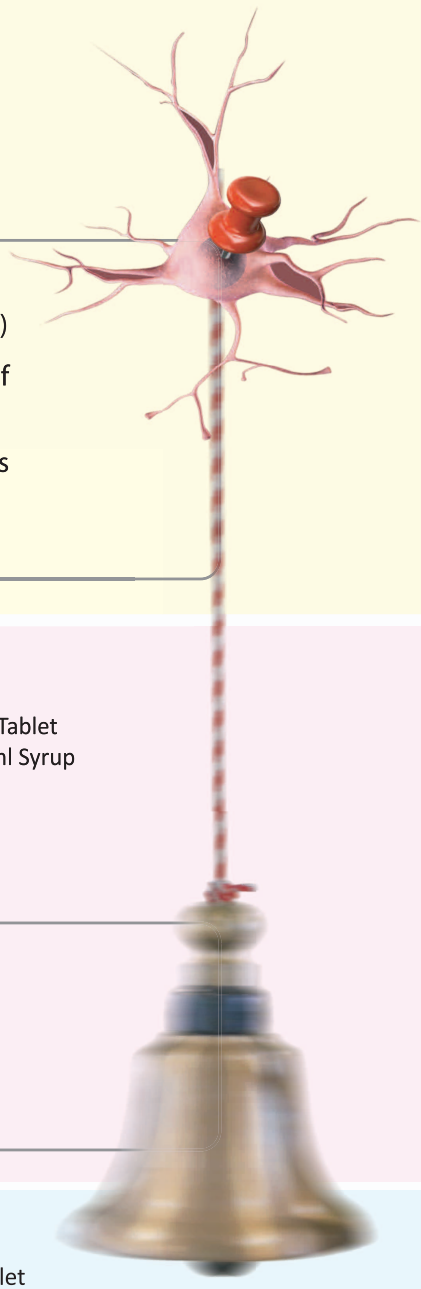

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