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MEDICAL MEMO

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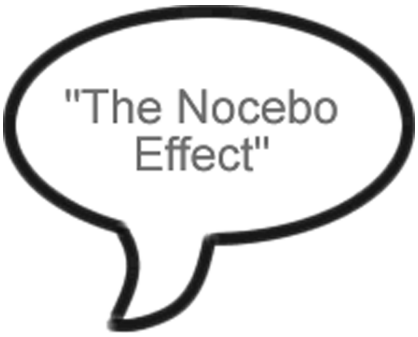
I Have heard of the Placebo Effect, but What is the NOCEBO Phenomenon ?

First, a brief review of the Placebo Effect. A **placebo** is an inert or inactive substance or treatment that the patient believes to be an active effective medicine or treatment. A placebo is essentially a fake medication or other treatment whose ingredients or actions are chosen to have no possible effects at all - good or bad. Sometimes they are called "sugar pills" to indicate they have no medicine in them. Non medicine treatments can also be placebos - for example a machine or a special "therapy" could be used as a placebo. **Thus, if you take a placebo it cannot, by its own direct chemical or medical action, either help or hurt you.** However; you may be helped by this "treatment", especially if you do not know it is a placebo, if the person or program providing it is a convincing powerful knowledgeable "expert" or if you expect it to help you. That is the placebo effect. Placebo treatments can thereby help a



patient, at least somewhat and for a while. Modern medical treatments, to be accepted and approved, must be shown in research studies to be significantly statistically more effective than placebo. If, for example, a placebo pill for depression helps 15% of people for 10 to 20 days (placebo effects generally wear off early) then a real medicine must do a lot better than that and not wear off while being taken to be accepted as "statistically significantly more effective than placebo". I, and physicians in general, do not use placebos except as part of a research study in which the placebo use is explained and agreed to by the study participant verbally and in writing.

The **Nocebo** phenomenon or effect is essentially the reverse of the placebo effect. **In the placebo effect you believe the "treatment" helps you while in the nocebo effect you think it hurts you or causes undesirable bad or side effects.** Thus, if you start a new treatment or medicine your worries or knowledge that the medicine could cause a side effect may cause you to be so sensitive or pay so much attention to body sensations that you imagine side effects or misinterpret the sensation as a side effect. Some people unknowingly experiencing the nocebo effect blame the medicine for what is actually a normal sensation or something that is only a symptom of an illness and not a side effect. Those most likely to experience the nocebo effect (false side effects) include: 1) those who expect side effects and are suggestible; 2) those who have

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often had true or nocebo side effects in the past; 3) anxious or depressed persons who somatize (experience emotions or stress as body discomforts) and show a heightened awareness of bodily sensation; and 4) those who are influenced by situational or symbolic factors such as the setting, the meaning of the illness or the treatment to the patient, the shape, size, or form of the pill, or even who or where or how the treatment is delivered. This explains why many doctors believe telling patients about most or all possible side effects too often leads patients to experience or think or fear they are experiencing those side effects. Some patients, and some parents of child patients, don't want to be told even common minor side effects for fear the information will become a self fulfilling prophecy.

The nocebo effect is much more common and much more of a problem than you might think. Remember that a placebo causes no good or bad effects directly on its own. In a double blind research study neither the patient nor the doctor knows till the end whether the participant is taking placebo or the real medicine. Both good and bad effects are closely monitored, recorded, and analyzed. Many such studies show that on placebo roughly 25% of healthy volunteers report headaches; 20% report fatigue, sedation, or insomnia; and 10-15% report nausea, appetite changes, various gastro-intestinal complaints, dizziness, nervousness, etc. The list goes on and on. Note that many of these complaints are generalized, diffuse, and not diagnostic of any specific condition. Thus many people stop, feel bothered by, or change treatments mainly because of this nocebo action. **When deciding whether a "side effect" is really the medicine what really matters is how the rates of side effects on placebo compare to what is reported by the people actually taking the medicine.** If those taking the medicines report a frequency that is at least 5 % more than the rate on placebo then it may actually be a medicine caused side effect - technically it is "more likely than with placebo". If the rate on the medicine is similar to the placebo rate then it probably isn't a side effect. If the rate is less than the placebo rate then it is unlikely a side effect and may even be a sign of a benefit of the medicine. **So when you want to know the side effects of a medicine it is generally best** not to read lists of possible side effects, or even side effect rates in brochures, advertisements, the text in package inserts, the PDR, or handouts from the pharmacy. **Instead,** look at the chart in the package insert, PDR, or a textbook that compares the percentage of patients or study participants who report each side effect on the placebo versus on the medication.

There are a number of ways to reduce the negative aspects of the nocebo phenomenon: I include the most common side effects and the important rare but severe (if any) side effects in my discussions and on my medicine chart handouts (available at my office or on my website, **www.leeheymd.com**) and try to put them in proper perspective. Supportive listening and reassurance when needed is often helpful. Understanding this nocebo phenomenon may also help the patient or parent or family. Starting cautiously at a low dose, sometimes very low, with small and slow conservative gradual increases to the low end of the therapeutic range often helps greatly. Being willing to revise the plan, reduce the dose, change the medicine, use psychotherapy or other therapies, or change the plan are also helpful. Close follow-up makes all this easier.

A New Trend in Medicines: What's so special about Lexapro?

Lexapro (escitalopram), **Focalin** (dexmethylphenidate), **Clarinex** (desloratidine), and **Nexium** (esomeprazole) are the single isomer newly available refined forms of the racemic medicines Celexa (citalopram), Ritalin (methylphenidate), Claritin (Clarinex), and Prilosec (omeprazole). They represent a new trend in pharmacology (the study and production of new medicines) toward even more specific and targeted medicines with even less side effects and interactions. This trend is being strongly encouraged by the FDA (Food and Drug Administration), reinforced by altruistic desires to more effectively relieve suffering, and is rewarded by extended patents for the companies who discover and develop these new medicines. **So what's the story behind these new options and what's in it for you?**

Many, but not all, molecules or chemicals whether developed in a chemistry lab or occurring naturally exist in or can be produced in 2 or more forms (isomers) whose structure differs only in how they look in three dimensional space. The key is whether one or more carbon atoms in the chemical's structure is bonded to other elements in a way that they can be rotated in space or that they rotate polarized light shown through the chemical. Such carbon (and occasionally nitrogen) atoms are referred to as a chiral center. If there is one chiral center there will be two isomers. If there are two chiral centers there will be four isomers - and so on. Although enantiomer is the proper term for these slightly variant forms, the term stereo isomers is almost as accurate - but for simplicity I'll use the term isomer in this article. These subtle spatial arrangement differences can make important differences in the chemical's function and its effects.

This is easier to understand than it may sound at first. Let's use your hands as an example. Although your right and left hands are both hands and appear essentially identical they are actually mirror images of each other. Your right hand does not exactly match your left (and vice versa) unless you look at it in a mirror. Thus, you have two forms, two structures, or isomers, of one object - the human hand. The human hand exists in 2 forms. This is also true of your ears, gloves, feet, shoes, and sides of your face, etc. What's really important though for our topic here is that the 2 forms (isomers) of this one object, your hand, function differently solely because of that seemingly minor mirror image difference. If you shake hands with someone you both use your right hands and they fit very nicely together. If you try to "shake" or join your left hand with your or someone else's

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right hand (or vice versa) it doesn't work. The same can be true of medicines. Very small differences in the three dimensional structure of the same medicine, neurotransmitter, receptor, etc., can greatly effect whether and how they work. It's similar to a very small change in a key causing that key to not fit into the lock. This is how neuro-transmitters carrying a message from one nerve cell to the next cell's receptor works - or doesn't work (fit). The name of these new isomer forms of the generic medicine is changed by adding a prefix showing whether the isomer is the left or right handed mirror image version or in which way polarized light shown thru the chemical is bent or turned (rotated).

Now, let's take the example of **Lexapro** and Celexa. Celexa is the brand name of the medicine citalopram which is used to treat depression and anxiety. Celexa is a racemic mix of the two isomer forms of citalopram. When all isomers are present it is called a racemic mix or racemate. It turns out that the left handed version of citalopram, named escitalopram, is more effective, potent, has even less negative interaction effects, may be faster to work, and has less side effects than either the right handed isomer version or the original citalopram (Celexa) parent mixture. Thus, the company which made Celexa has used advanced techniques to produce pure escitalopram, which they brand named Lexapro. Lexapro has been approved by the FDA based on effectiveness and safety studies, the company gets an extended patent, and we get an improved refined form of an already good medicine. Of course, time and clinical experience will reveal just how good it is. Lexapro is expected to be available in, or soon after, September 2002.

The same or similar scenarios have led to **Focalin** for ADHD, Clarinex for allergies, and Nexium for GERD (gastro-esophagael reflux disorder). Others are in development and more are certain to come. Each brings certain expected advantages over the original. These and other single isomer medicines represent an expanding future trend because in general they have several potential advantages over racemic mixes: they are less complex, have more selective effects and functions, have less interactions, and bring potentially improved benefits. This does not always pan out, however. The makers of Prozac (the generic fluoxetine is available), which is a racemic mix, studied the isomers and found the mix actually had less side effects than the pure isomer forms and therefore stayed with their original mix. Wellbutrin (generic buproprion available) and Effexor (venlafaxine) are also racemic mixes. Several single isomer medicines have been available for years. Examples include morphine, Paxil, and Dexedrine. Each has been used effectively for many years. Dexedrine is the brand name of the single isomer generic medicine dextro-amphetamine while its isomer levo-amphetamine is not used separately. "Dextro" refers to the right handed isomer and "levo" is the left handed isomer of the racemic mix amphetamine. **Adderall** is a combination of these 2 isomers of dextro and levo-amphetamine. The levo isomer gives the combination a longer effect while the dextro version gives more focused dopamine action. Thus, you can see that this whole growth area of single and mixtures of isomers is not totally new but is an expanding and useful trend.

Those who wish to learn more are referred to the April 2002 supplement of the journal CNS Spectrums or to the stereo chemistry chapter of any organic chemistry textbook.

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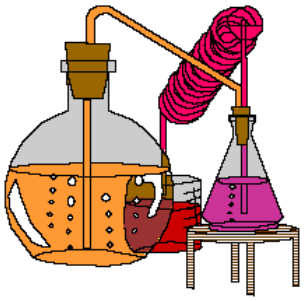
New Medicines, New Doses, New Forms



There are several new options available since the first of this year. Each of these are included in the updated medication charts on my website, **www.leeheymd.com.**

First, new generics: regular (not the XR form) **Adderall** has recently become available in a generic version. Buspar (buspirone), Luvox (fluvoxamine), Prozac (fluoxetine), and the regular form (not SR) of Wellbutrin (buproprion) have been available for several months to a year. All of these generally work well although a few people do better with the brand versions.

New convenient doses: **Wellbutrin SR** has added a 200 mg pill simplifying and saving money for those who were taking either two 100 mg pills in the morning or two twice a day. Still available are 100 SR and 150 SR sizes. **Concerta** has come out with a 27 mg pill which is halfway between their 18 and 36 mg sizes. Now if only they'll produce a 45 mg to fit between their 36 and 54 mg sizes... **Adderall XR** has brought out 15 XR, 25 XR, and plan a 5 XR soon to go with their already available 10 XR, 20 XR, and 30 XR capsules - now that's convenient dosing! Each of these three medicines is a longer duration version of the original and because of how the pill or capsule is made they cannot be split - thus more dose sizes is a plus.

New forms of existing medicines: Paxil has added a longer duration form called **Paxil CR** (controlled release) which gives a smoother more consistent level in the body which should lessen side effects and also lessen any discontinuation (like but not "withdrawal") effects. Two medicines now have oral dissolving forms - **Remeron Solutabs** and **Zyprexa Zydis** - which eliminate pill swallowing problems without using a liquid form. **Ritalin LA** is a "long acting" capsule form of Ritalin designed to release half its medicine right away and half about four hours later. Thus it is another stimulant option designed to avoid having to take a lunch time dose. **Focalin** (dexmethylphenidate) is the right handed isomer form of methylphenidate (Ritalin, Methylin) - see the "New Trend - Lexapro" article also in this newsletter. Focalin provides a refined form of the original Ritalin, making Focalin a better match for some people. **Lexapro** is a refined Celexa which is further described in the just mentioned article.

New Medicines: **Gabatril** (the generic name is tiagabine) is a relatively new anti-convulsant (medicine to control seizures) which may have use in psychiatry because of its unique exclusive action as a GABA (the neuro-transmitter Gamma Amino Butyric Acid) reuptake inhibitor. In other words it increases GABA in the same way the SRI's (serotonin reuptake inhibitors) like Prozac, Paxil, Zoloft, Luvox, and Celexa work to increase serotonin. So far it is showing some tentative promise as an anti-anxiety medicine and is being studied as a mood stabilizer. **Trileptal** (oxcarbazepine) is chemically similar to Tegretol (carbamazepine) but without Tegretol's many undesirable interactions with other medi-

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New Medicines

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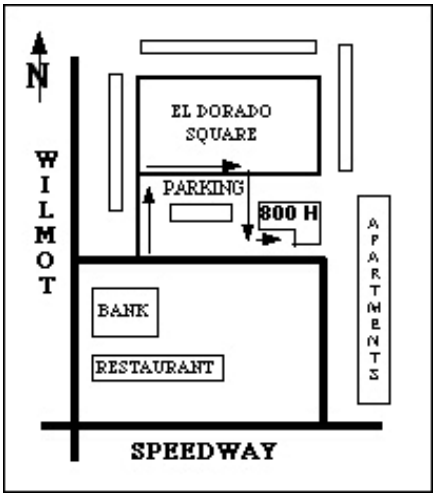
cines and without its possible blood count side effects. It is likely to be helpful, as is Tegretol, as a mood stabilizer and temper medicine but with a better side effect profile.

Coming Medicines:

There are many medicines on the way in various stages of development. One can never be sure how good they are until they actually are approved by the FDA, are brought out for use by doctors and patients, and time passes to build a track record. One exciting coming option is **Atomoxetine** (no brand name yet) which is the first non-stimulant to, in initial studies, show effectiveness in ADHD comparable to the stimulants (Ritalin, Adderall, etc.). It may also have benefit for depression. A skin patch form of Ritalin (methylphenidate) to be called something like **MethyPatch** is being tested. The novel norepinephrine increasing antidepressant **Vestril (reboxetine)** is still in the pipeline although its release has been delayed.



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