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MEDICAL MEMO

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The Safety of Antidepressants in Children

In mid October 2004 the US Food and Drug Administration (FDA) announced new warnings and precautions to strengthen safeguards for children and adolescents treated with antidepressant medications. A "black box" warning is to be added to the package inserts and a Medguide (small information pamphlet) is to be handed out when the prescription is picked up at the pharmacy. The caution and added information is to make parents aware of the possibility of increased suicidal thinking and behavior that may occur in a small percentage of children and adolescents especially during the early phase of treatment. Monitoring and communication between parent, patient, and doctor is advised.

SRI (Serotonin Reuptake Inhibitors) antidepressants include Prozac (generic is fluoxetine), Zoloft, Paxil (paroxetine), Luvox (fluvoxamine), Celexa, Lexapro, and to some degree Effexor, Cymballta, and Anafranil (Clomipramine). These are all used for various anxiety disorders as well as depression. Other non SRI antidepressants include Wellbutrin (buproprion), Remeron (mirtazapine), nefazodone, trazodone, maprotiline, the tricyclics (imipramine, desipramine, doxepin, amitriptyline, nortriptyline), the MAOI's, and a few others. Please see my medicine charts for more information. Let's put this all in perspective. The media response is, in this doctor's opinion, overblown. For those of us who have been for years treating kids for depression and anxiety none of this is new information. We have been educating our patients and their families about benefits, possible side effects, and risks for years. The following are the important details regarding the new FDA action.

The FDA and a team at Columbia University recently reported that in a review of 24 studies using antidepressants (mostly SRI's) in over 4400 youth (children and teen) patients the rate of suicidal thoughts or behavior amongst youth taking placebo (fake pills) was 2 % and that the rate amongst youth taking antidepressants was 4 %. There were **no** completed suicides in any of these 4400 patients. Thus, the actual risk was that 2 of every 100 youth who took antidepressants had suicidal thoughts or behavior possibly related to the medicine and that 98 out of every 100 did not.

How do we make sense of this information? There are several ideas. First must be the recognition that suicide thoughts or even certain self harmful behaviors do not necessarily indicate serious risk or danger. Suicide ideas or even certain acts do **not** equal and rarely lead to completed suicide. Research studies are set up to, if anything, over identify and react to the slightest potential negative or side effect. Every year in the US there are several hundred youth considering suicide for every suicide attempt and there are well over a hundred attempts for every completed youth suicide. One NIH (National Institutes of Health) funded study of suicidal ideation in teens found that a full 25% of all high school students have thoughts about suicide and 1% report enough of an attempt to require medical care each year. These real world high percentages far exceed what was reported in these medicine studies. Yearly actual deaths by suicide in youth have been in the range of 1 to 2 per 10,000 (.01 %). The no deaths in 4400 youths in the medicine studies is the more important number and fits the known true risk. These numbers explain why many doctors believe both the FDA and media have again over-reacted.

It has long been known that one of the highest risk times for suicide is when someone who has been seriously depressed has recovered enough to now have the energy to act while not yet being recovered enough to no longer have suicidal thoughts, impulses, or intent. In a few rare instances the medicine or other treatment(s) or time restores energy before removing enough depression to stop the self destructive thoughts or behaviors that are a common

part of depression. This is a main reason why appointments and monitoring at home are often more frequent in the early stages of recovery.

A related possible explanation is that if the patient has energizing, activating, disinhibiting. emboldening behavioral side effects their usual behavior or typical personality may temporarily change enough that they may do things they wouldn't normally do. This is not new information to my patients or to psychiatrists. For example, see my Medical Memo newsletter Summer 1999 issue entitled "What Are Behavioral Side Effects?" This information was first broadly addressed with regard to Prozac by 1992. Because this happens more with some SRI's than others and generally not with non SRI's psychiatrists take this into account along with other factors when discussing and choosing which, if any, medicine to select. Although I have not seen this energizing activating side effect result in suicidal or violent behavior I think this is the unfortunately blown out of proportion kernel of truth behind the recent FDA warning and media sensationalism.

Another possible explanation for an increase in self harm ideas or behavior is that the diagnosis is in error and therefore the medicine choice is not optimal. A possible example is that the patient actually has Bipolar Disorder and that using an antidepressant instead of a mood stabilizer may cause switching into mania or rapid cycling between depression and mania. This is more of a concern with the older tricyclic antidepressant group than with SRI's and other newer antidepressants. Follow up appointments are wise for many reasons. One reason is to assess over time whether the diagnosis is right, whether there are other factors or conditions to treat, and to be more sure response to treatment is as expected.

Considerable special interest, political agendas, financial, and legal (such as lawsuits) factors have over the years influenced FDA actions counter to common sense scientific and clinical experience. The horrendous and traumatic experience of having your child die by suicide has led many parents to advocate for awareness and treatment. A few parents whose children died while on antidepressants have strongly questioned whether the treatment (rather than the illness) led to the suicide. Some groups use and distort such tragedies to advocate an anti medicine and anti treatment agenda. In the last 10 years since these medicines have become more broadly available for youth there has been a large very gratifying decrease in the suicide rate amongst our youth resulting in literally thousands of saved lives and many many more improved lives. Another FDA error is lumping all "antidepressants" into the FDA caution (to avoid a singled out company suing the FDA?) when mainly the SRI's should be considered. Another example of over-reaction error is the British version of the FDA advising only using Prozac in youth despite the fact these type concerns were first brought up in adults on Prozac in 1992 (and shown to be overblown. Pharmaceutical companies have engendered some mistrust by not releasing all study data. The FDA and Congress have erred in not following medical groups' urging to require studies of all age and ethnic groups, both sexes, and both in and outpatients before granting medicine approvals. In past decades the FDA approved many medicines for use in youth without any studies in youth having been done – they were "grandfathered in". Now FDA approvals for youth require studies in youth although medicines can be approved for adults without also studying them in kids. Companies are left to choose whether to do these complicated and expensive studies if they want an "indication" (approval) for a certain condition in a certain age range. The result is that for youth there is a mishmash of approvals that make no real clinical sense. For example, Prozac (fluoxetine) is approved only for depression down to 6 years old while Zoloft and Luvox (fluvoxamine) are approved only for OCD (Obsessive Compulsive Disorder) down to 8 years old while Celexa (citalopram), Paxil (paroxetine), Lexapro and Effexor are not approved at all for under 18. Thus, likely equally safe medicines are not approved for youth and other much less safe ones are approved to as young as 6 months of age! Clinical experience indicates that all the SRI's are comparably effective for depression, anxiety, panic and OCD with differences mainly in some side effects, interactions, and some individuals having unique response to one or another SRI. Fortunately for patients, once a medicine is approved by the FDA for any age and any condition it can be used by doctors as clinically appropriate. These realities are true for all specialties in all areas of medicine.

Summary: When prescribed and monitored appropriately for Depression, Obsessive Compulsive Disorder, and various Anxiety and Panic Disorders these medicines can be extremely helpful in restoring function, helping youth (and adults) live normal lives, and save many lives.

Cymbalta, A New Medication Option

In the fall of 2004 the new SNRI (serotonin and norepinephrine reuptake inhibitor) Cymbalta (duloxetine) was approved by the FDA and became available for use in adults for Depression and diabetic neuropathy pain. It is also expected to prove helpful for anxiety, panic, OCD, and possibly for other physical pain disorders in all age groups. Cymbalta combines the serotonin increasing action of SRI's (Prozac, Zoloft, Celexa, etc) with the norepinephrine increasing action of Wellbutrin (buproprion) and Strattera (atomoxetine). This dual action makes Cymbalta a broader spectrum potentially more effective medicine. Some such medicines with multiple actions help pain and physical symptoms of depression more than single action options. Cymbalta is most similar to Effexor (venlafaxine) which is also a dual acting SNRI. However, Cymbalta's dual effect begins right away while Effexor has only the serotonin benefit until the dose is raised high enough for the norepinephrine effect to kick in. Dual action also means more potential side effects than single action meds. These include possible negative side effects on nausea, energy, sleep, sexual effects, sweating, blood pressure, or weight.

Taking it with or soon after food and starting at a low dose lessen the chance of nausea. Headaches may be less common with Cymbalta than with placebo (ie, it may help prevent headaches). Interactions with other medicines are relatively few. Alcohol is best avoided. Like all medicines it is to be avoided if possible in pregnancy and probably in breast feeding. Capsules are available in 20, 30, and 60 mg doses. Dose ranges from 20 to 120 mg a day taken once or split up twice a day with the most common expected dose around 60 mg a day. As with other antidepressant and most anti-anxiety medicines it is best tapered on and off – not stopped suddenly. Like other such medicines, although its effect may begin in the first few days, generally it takes 1 to 3 weeks to kick in and a good month to see what a given dose will do. Cymbalta, which some jokingly say sounds like the name of a character from Lion King, is a favorably anticipated new option whose overall value will become clearer with time. Please see my website (leeheymd.com) medicine charts for more information.

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