NEWS IN BRIEF

EXPANDING THE BLACK BOX – DEPRESSION, ANTIDEPRESSANTS, AND THE RISK OF SUICIDE

In May 2007, the FDA ordered that all antidepressant medications carry an expanded black-box warning incorporating information about an increased risk of suicidal symptoms in young adults 18 to 24 years of age. Since October 2004, antidepressants have been required to have a black-box warning indicating that they are associated with an increased risk of suicidal thinking, feeling, and behavior in children and adolescents. The new warning also states that there is no evidence of an increased risk for adults older than 24 years of age and that the risk is actually decreased for adults 65 years of age or older. The label states that "depression and other serious psychiatric disorders are themselves associated with increases in the risk of suicide," and implies that there is risk in not using the very medication being warned about.

The notion that antidepressants might be associated with an increased risk of suicidality in some patients is not new. In the first few weeks of treatment with antidepressants, some patients become "activated" — energised and agitated — before their depressed mood lifts, and that combination makes them more likely to act on preexisting suicidal impulses. But because suicidal thinking, feeling, and behavior are core symptoms of depression, there is no way to know whether suicidal symptoms that develop during treatment are due to the underlying illness or the medication.

The FDA considered the results of comprehensive meta-analyses of an enormous data set on 99,839 participants in 372 randomised clinical trials of antidepressants conducted by 12 pharmaceutical companies during the past two decades. No increased risk of suicidal behavior or ideation was perceptible when analyses were pooled across all adult age groups. However, in age-stratified analyses, the risk for patients 18 to 24 years of age was elevated, but not significantly (odds ratio, 1.55; 95% confidence interval, 0.91 to 2.70). However, the trend across age groups toward an association between antidepressants and suicidality was convincing when superimposed on earlier analyses of data on adolescents from randomised, controlled trials.

However, there are some shortcomings in the meta-analyses considered by the FDA. The studies were designed primarily to assess short-term efficacy, not long-term safety. The suicidal symptoms came from adverse-event reports, and this subject to ascertainment bias. Participants who report common side effects would be more likely to be asked about other adverse effects and might be more likely to report suicidal symptoms. Also, younger participants might be more likely than older participants to report adverse events. The meta-analyses also ignored attrition, which might have varied with age.

But the greatest difficulty for interpretation is whether suicidality is caused by the disease or the treatment. About 20% of the data came from studies of treatment for nonpsychiatric indications (for example, smoking cessation, insomnia) and for nonbehavioral indications (for example, fibromyalgia, diabetic neuropathy), but these data were not included in the

primary analyses. The risk per person-year of treatment was substantially lower in trials for nonpsychiatric indications, suggesting that depression played a key role in suicidality and that antidepressants do not themselves generate new suicidal symptoms.

Whether the new warning will do more good than harm is not clear. There are already some signs that the warning will discourage depressed patients and their families from seeking treatment and frighten physicians away from prescribing antidepressants.

There may be controversy about the risk posed by antidepressants, but there is none about the risk associated with untreated depression. The authors suggest that the real killer is untreated depression, and the possible risk from antidepressant treatment is dwarfed by that from the disease. But they warn that clinicians need to tell their depressed patients that some people who take antidepressants have an increase in suicidal symptoms, especially early in treatment, and they need to follow their patients very closely during the first four to six weeks of treatment.

(Source: Friedman RA, Leon AC. New England Journal of Medicine 2007 June 7;356(23):2343-6)

ANTIPSYCHOTIC DRUG USE AND MORTALITY IN OLDER ADULTS WITH DEMENTIA

In April 2005, the US FDA issued a public health advisory that the use of atypical antipsychotics to treat elderly patients with dementia was associated with an increased risk for death compared with placebo. In June 2005, Health Canada issued a similar warning. These warnings stem from reviews of RCTs that involve the atypical agents risperidone, olanzapine, quetiapine, and aripiprazole. The mortality rate was approximately 1.6 to 1.7 times higher than with placebo and was greater with antipsychotics than with placebo in 15 of the 17 trials reviewed by the FDA. The warnings extend to all currently available atypical antipsychotics. Other publications have provided support for these warnings and have raised further safety concerns about older conventional antipsychotics.

The authors set out to examine the association between treatment with antipsychotics (both conventional and atypical) and all-cause mortality. They performed a population-based, retrospective cohort study in Ontario, Canada. Older adults with dementia were followed between 1 April 1997 and 31 March 2003. The risk

for death was determined at 30, 60, 120, and 180 days after the initial dispensing of antipsychotic medication. Two pairwise comparisons were made: atypical versus no antipsychotic use and conventional versus atypical antipsychotic use. Groups were stratified by place of residence (community or long-term care). A total of 27,259 matched pairs were identified. New use of atypical antipsychotics was associated with a statistically significant increase in the risk for death at 30 days compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio, 1.31 [95% CI, 1.02 to 1.70]; absolute risk difference, 0.2 percentage point) and the long-term care cohort (adjusted hazard ratio, 1.55 [CI, 1.15 to 2.07]; absolute risk difference, 1.2 percentage points). Excess risk seemed to persist to 180 days, but unequal rates of censoring over time may have affected these results. Relative to atypical antipsychotic use, conventional antipsychotic use was associated with a higher risk for death at all time points. Sensitivity analysis revealed that unmeasured confounders that increase the risk for death could diminish or eliminate the observed associations. The authors concluded that atypical antipsychotic use is associated with an increased risk for death compared with nonuse among older adults with dementia. The risk for death may be greater with conventional antipsychotics than with atypical antipsychotics.

The study has important limitations. First, the authors used observational study techniques. Second, they did not examine the risk for death posed by individual antipsychotic drugs. Third, they could not examine the causes of death. Fourth, they did not examine dose-response relationships, given the complexity of our study design and changes in dosages over time. Fifth, they could not match all potentially eligible patients. Finally, the study was restricted to older adults with dementia, and safety for other indications for the use of antipsychotics (for example, schizophrenia, delirium) were not studied.

Several plausible mechanisms can be proposed. First, antipsychotics may prolong the QT interval, predisposing patients to arrhythmias and sudden cardiac death. Second, sedation and accelerated cognitive decline brought on by exposure to antipsychotics may increase the risk for aspiration syndromes and choking. Third, several studies have found a link between atypical antipsychotic use and venous thromboembolism. Fourth, a risk for cerebrovascular events may be associated with antipsychotic use, although this risk has been questioned. Finally, antipsychotics may contribute to events that are not initially recognised as the first

step in a sequence that promotes premature death, such as falls leading to hip fractures. Although details are limited, deaths in the RCTs seem to have been primarily related to cardiac arrhythmias and aspiration pneumonia.

The authors suggest that their results have important implications for clinical practice. First, conventional antipsychotics seem to be associated with a higher risk for death than are atypical antipsychotics. Second, the estimated mortality rate among study participants was high, especially in the long-term care setting. Third, In FDA and Health Canada reviews, the risk for death seemed to be a class effect with all atypical antipsychotics studied. Thus, switching between individual atypical antipsychotics in an attempt to modify the risk for death cannot be recommended. Finally, the role of atypical antipsychotics in the management of behavioral and psychological symptoms of dementia must be carefully reviewed. The authors point to approach used by others that limits the use of these drugs to situations in which "there is an identifiable risk of harm to the patient or others, when the distress caused by symptoms is significant, or when alternate therapies have failed and symptom relief would be beneficial." Because the risk for death associated with antipsychotics develops quickly and may persist for up to six months, clinicians must re-evaluate benefits and risks frequently and consider discontinuation of treatment when appropriate.

(Source: Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N, Gurwitz JH, Rochon PA. Ann Intern Med. 2007 June 5; 146(11):775-86)

EFFECT OF ROSIGLITAZONE ON THE RISK OF MYOCARDIAL INFARCTION AND DEATH FROM CARDIOVASCULAR CAUSES

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus. The authors performed a meta-analysis of 42 studies with a duration of more than 24 weeks, which used a randomised control group not receiving rosiglitazone, and in which the outcome data for myocardial infarction and death from cardiovascular causes were available. The mean age of the subjects was about 56 years. The mean baseline glycated hemoglobin level was about 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06). The authors concluded that rosiglitazone was associated with a significant increase in the risk

of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. The study was limited by a lack of access to original source data.

Rosiglitazone is one of the thiazolidinediones used to lower blood glucose levels in patients with type 2 diabetes mellitus. Three such agents have been introduced: troglitazone, which was removed from the market because of hepatotoxicity, and two currently available agents, rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda). The thiazolidinediones are agonists for peroxisome-proliferator-activated receptor (PPAR-). PPAR- receptors are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose primarily by increasing insulin sensitivity in peripheral tissues.

The mechanism for the apparent increase in myocardial infarction and death from cardiovascular causes associated with rosiglitazone remains uncertain. One potential contributing factor may be the adverse effect of the drug on serum lipids. The FDA-approved rosiglitazone product label reports a mean increase in low-density lipoprotein (LDL) cholesterol of 18.6% among patients treated for 26 weeks with an 8-mg daily dose, as compared with placebo. The thiazolidinediones are also known to precipitate congestive heart failure in susceptible patients. They also produce a modest reduction in the hemoglobin level, and in susceptible patients, this may result in increased physiological stress, provoking myocardial ischemia.

Rosiglitazone is not the first PPAR agonist that has been reported to increase adverse cardiovascular events. Muraglitazar, an investigational dual PPAR- and PPAR- agonist, increased adverse cardiovascular events, including myocardial infarction, during phase two and three testing.

PPAR agonists such as rosiglitazone have very complex biologic effects, resulting from the activation or suppression of dozens of genes. The biologic effects of the protein targets for most of the genes influenced by PPAR agonists remain largely unknown. Accordingly, many different and seemingly unrelated toxic effects have emerged during development of other PPAR agents.

The question as to whether the observed risks of rosiglitazone represent a "class effect" of thiazolidinediones must also be considered. However, pioglitazone appears to have more favourable effects on lipids, particularly triglycerides, than does rosiglitazone. ∎

(Source: Nissen SE, Wolski K. New England Journal of Medicine 2007; 356:2457-2471)