

# SCORE Newsletter FAQs

## Frequently Asked Questions - Summer 2009

SOUTH CAROLINA OFFERING  
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*SCORxE Newsletter FAQs shares highlights of answers to questions specifically asked by individual providers in the community. Such focus is not intended as an endorsement by SCORxE since a complete overview of a medical condition or situation is beyond the scope of the condensed newsletter format. The reader is responsible for using professional judgment in analyzing and interpreting this information before accepting and utilizing it in clinical practice.*

### **What are the safety concerns that have been reported for varenicline (Chantix®), a drug used to aid smoking cessation?**

On July 1, 2009, the FDA announced that it is requiring manufacturers of Chantix® and Zyban® (bupropion) to include a Boxed Warning and update their patient Medication Guides to highlight the risk of serious mental health events (including behavioral changes, depressed mood, hostility, and suicidal thoughts) while taking these smoking cessation drugs. Wellbutrin® (bupropion) and generic bupropion products will also be required to add similar information on the risk of mental health events to the Boxed Warning already in place for suicidal behavior in treating psychiatric disorders. The added warnings are based on the continuing review of post-marketing adverse event reports for varenicline and bupropion received by the FDA. While these reports suggest a possible link to suicidal events, further research is under way to better evaluate causality and magnitude of risk with varenicline use, particularly in populations with pre-existing psychiatric conditions.

The neuropsychiatric symptoms reported with varenicline usually developed during treatment, but sometimes developed following its discontinuation. It is unknown if the symptoms may have occurred as a result of nicotine withdrawal in some patients; others who developed neuropsychiatric symptoms had not yet discontinued smoking. While worsening of pre-existing psychiatric illness has been reported in the post-marketing experience, the safety and efficacy of varenicline in patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder remain unknown since these patients were excluded from the pre-marketing studies.

Numerous reports of serious injury linked to traffic accidents or falls have led three US government departments to limit or ban the use of varenicline. The Federal Aviation Administration has banned its use by airline pilots; the Department of Transportation has limited its use among truck drivers; and the Department of Defense has prohibited its use by aircraft and missile crews.

### **What is the published evidence to support the increased risk of sudden cardiac death associated with the use of both first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs)?**

A retrospective cohort study by Ray and colleagues published in the *New England Journal of Medicine* (2009) evaluates the risk of sudden cardiac death associated with FGAs and SGAs in a Medicaid enrolled population. Results show a similar, dose-related increased risk of sudden cardiac death for current users of FGAs (1.99 [1.68-2.34]) and SGAs (2.26 [1.88-2.72]). An accompanying editorial by Schneeweiss and Avorn puts the findings into perspective and suggests a risk-management program; namely, routine electrocardiogram monitoring at initiation and dose increases as well as more judicious use of antipsychotics in vulnerable populations.

The American Psychiatric Association (APA) has since issued guidance on the topic that highlights methodologic limitations of the study as well as a lack of data regarding the utility and cost-effectiveness of serial QTc measurement in antipsychotic-treated patients as recommended by Schneeweiss and Avorn. With regard to cardiac safety, the APA recommends that clinicians continue to follow current practice guidelines for the work-up and management of psychotic patients.

### ***Is quinine still available for the treatment of nocturnal leg cramps? Are there effective alternative treatments?***

The FDA banned over-the-counter quinine sulfate formulations in 1994, recommended against its use for muscle cramps in 1995, and removed all formulations off the market in 2006, except for Quaaluan® which is only FDA-approved for the treatment of malaria. Quinine use has been associated with serious, occasionally fatal side effects such as hypersensitivity reactions, hepatitis, cardiac arrhythmias, and cinchonism (quinine poisoning).

Quinine has long been used for the treatment of nocturnal leg cramps, and it remains the best proven pharmacologic intervention despite more recent, less impressive results. There is scant evidence to support the use of other pharmacologic treatments. Open-label studies suggest that gabapentin (Neurontin®), 300 to 900 mg daily, or verapamil (Calan®, Verelan®, Isoptin SR®) 120 mg daily may reduce nocturnal leg cramps. There are anecdotal reports of carbamazepine (Tegretol®) and phenytoin (Dilantin®) as treatment for leg cramps. Various supplements, such as magnesium, sodium and calcium, have been suggested for the treatment of nocturnal leg cramps. The best evidence favors magnesium for pregnant women with leg cramps, but not for other people. Vitamin E up to 1000 IU daily may be helpful for leg cramps in patients with liver or renal disease. Preliminary data suggest that Pycnogenol® (a natural plant extract from the bark of the maritime pine tree found exclusively along the coast of southwest France and not to be confused with names of grape seed extracts) 200 mg daily may be helpful for treating muscle cramps. Consumers have also reported benefits with homeopathic formulations containing quinine and other herbs (e.g., Leg Cramps®); however, these products have not been scientifically evaluated.

### ***What is the role of second generation antipsychotics (SGAs) such as aripiprazole (Abilify®) in the treatment of major depressive disorder (MDD)?***

Evidence suggests that SGAs can effectively augment antidepressants in patients with MDD who do not fully respond to antidepressant monotherapy. The *SCORxE Evidence-Based Best Practices for the Treatment of Non-Psychotic Major Depressive Disorder (MDD) in Primary Care in South Carolina* lists SGAs as third-line strategy (i.e., Stage 3) in the treatment algorithm. Other augmentation strategies are listed in various stages of the algorithm.

Two SGAs have recently obtained FDA-approval as augmentation strategies. Aripiprazole is FDA-approved to augment antidepressants for the treatment of MDD, while the olanzapine/fluoxetine combination product (Symbyax®) is specifically FDA-approved for treatment-resistant depression (TRD), usually defined as a failure to respond to two or more antidepressants. Quetiapine (Seroquel XR®) may soon get final FDA-approval since a FDA panel recently deemed “acceptable” its efficacy and safety as augmentation in MDD. Potential benefits of SGA augmentation should be weighed in view of potential risks. All SGAs carry a risk, albeit low, of causing tardive dyskinesia. Several SGAs are associated with weight gain and metabolic syndrome. Other serious side effects, such as a possible increased risk of sudden cardiac death, may also exist. Finally, cost is another factor to consider since none of these medications (except for risperidone [Risperdal®]) are available as generics.

**References for this issue and additional information are available upon request from your SCORxE consultant, or send an email to [SCORxE@sccp.sc.edu](mailto:SCORxE@sccp.sc.edu).**



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