Prescribing....

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Varenicline

- Varenicline is the newest licensed product for smoking cessation in adults.
- There have been some concerns that it may increase the risk of depression and suicides.
- A new study provides more reassurance to clinicians and patients on its neuropsychiatric safety.
- As always any potential adverse effects should be balanced against theconsiderable benefits of smoking cessation to the individual and the community.

What is the background to this ?

Varenicline is licensed for smoking cessation in adults. In the twelve months ending May 2015 there were 566 prescriptions dispensed on the islands for varenicline at a cost of £24,301 plus grants, charges and fees. The summary of product characteristics states that smokers should set a date to stop smoking, and treatment with varenicline should start 1 to 2 weeks before this date and continue for 12 weeks in total. The summary of product characteristics highlights that smoking cessation therapies are more likely to succeed in people who receive additional advice and support. Furthermore the benefits obtained in the landmark trials were only achieved in the context of support.

In 2008, the MHRA advised that depression and suicidal thoughts and behaviour had been reported in people using varenicline, including those with no pre-existing psychiatric conditions. In 2009, a UK cohort study found no clear evidence that varenicline was associated with an increased risk of fatal or non-fatal self-harm, depression or suicidal thoughts (Gunnell et al. 2009). The MHRA reviewed this study and commented that it provided some reassurance about the risk of varenicline on suicidal behaviour. However, the warnings in the summary of product characteristics for varenicline were not amended.

What is the current advice ?

Clinicians should be aware of the possible emergence of significant depressive symptoms in people using varenicline as part of a smoking cessation attempt. Varenicline should be stopped immediately if agitation, depressed mood or changes in behaviour or thinking are observed that are of concern for the doctor, the user, family or caregivers, or if the user develops suicidal ideation or suicidal behaviour. See the summary of product characteristics for more information on the neuropsychiatric adverse effects of varenicline.

The NICE guideline on smoking cessation services provides more information on the use of nicotine replacement therapy, varenicline and buproprion to aid smoking cessation, along with giving advice, encouragement and support, or referral to a smoking cessation service. The NICE pathway on smoking brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.

And the new evidence ?

A systematic review and meta-analysis has assessed the risk of neuropsychiatric adverse events and death in published placebo-controlled, randomised controlled trials (RCTs) of varenicline 1 mg twice daily (Thomas et al. 2015). Of the 44 studies identified, 39 were included in the meta-analysis (n=10,761).

Two people in the varenicline group (n=5817) committed suicide, and 2 people in each of the varenicline group and the placebo group (n=4944) attempted suicide. There was no significant difference between the groups in the primary outcomes of risk of suicide or attempted suicide (odds ratio [OR]=1.67, 95% confidence interval [CI] 0.33 to 8.57; 31 RCTs, n=9830), suicidal ideation (OR=0.58, 95% CI 0.28 to 1.20; 20 RCTs, n=4990) or depression (OR=0.96, 95% CI 0.75 to 1.22; 31 RCTs, n=9843). There was also no difference between the groups in the risk of death, irritability, aggression or somnolence. Compared with placebo, varenicline was associated with an increased risk of sleep disorders, insomnia, abnormal dreams and fatigue, but a reduced risk of anxiety.

Subgroup analyses found no evidence for a variation in depression and suicidal ideation by age, gender, ethnicity, smoking status, presence or absence of psychiatric illness, or type of study sponsor.

The authors concluded that these results provide some reassurance for users and prescribers about the neuropsychiatric safety of varenicline. However, inevitably the study has several limitations. For example, it was not possible to determine whether differences in adverse events were because of greater smoking cessation rates in the varenicline group compared with placebo. Also, biases such as reporting and publication bias could not be excluded.

So what ?

This study provides a good quality analysis of the risk of neuropsychiatric adverse events associated with varenicline, in the context of participation in clinical trials. It backs up the evidence for no association of varenicline with neuropsychiatric events from observational studies.

It should be noted that included trials varied in their exclusion criteria, with some excluding people with a history of depression, suicidal ideation or suicide attempts. Additionally, the authors note the small number of attempted suicides and suicides mean an effect of varenicline on suicide rates cannot be completely ruled out. Variability of definitions, and detection, of suicidal ideation and suicide in both RCTs and observational studies is a known problem.

The spontaneous case reports that led to the initial concerns over varenicline have confounding factors, such as the potential neuropsychiatric effects of smoking cessation itself, concomitant medicines, alcohol, and a previous history of depression. But the rare possibility that varenicline might cause severe neuropsychiatric reactions in susceptible individuals cannot be eliminated. Nevertheless, this meta-analysis provides additional reassurance that the overall risk of suicide with varenicline is negligible in the majority of people without potential risk factors.

Short-term rare risks always need to be balanced with the long-term risks associated with smoking, as well as the risks and effectiveness of other smoking cessation therapies. However, prescribers should be aware of the manufacturer's warnings, and counsel people about the potential for rare neuropsychiatric symptoms, particularly in those with risk factors (such as a history of psychiatric illness). It would seem wise that patients should be informed in a balanced way about the evidence, but also encouraged to report any concerns they may have.

References : NICE Medicines Evidence Summary 2015

Written by: Geraldine O'Riordan, Prescribing Advisor Tel: 01481-732460