Risk of neuropsychiatric adverse events with varenicline

A meta-analysis found no increase in the risk of suicide or attempted suicide, suicidal ideation or depression with varenicline compared with placebo. However, prescribers should be aware that the warnings on neuropsychiatric adverse events remain in place within the summary of product characteristics for varenicline.

Overview: Varenicline is licensed for smoking cessation in adults. According to the summary of product characteristics, 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. For people who have stopped smoking after 12 weeks, an additional 12-week treatment course may be considered for maintaining abstinence.

Varenicline may also be used for a gradual approach to stopping smoking for people who are unable or unwilling to stop abruptly. Smoking should be reduced during the first 12 weeks of varenicline treatment and stopped by the end of that period. Treatment should subsequently be continued for a further 12 weeks. The summary of product characteristics highlights that smoking cessation therapies are more likely to succeed in people who receive additional advice and 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.

Current advice: NICE recommends that varenicline is a possible treatment to help smokers who want to stop smoking. It should normally be used only as part of a programme that includes advice from a healthcare professional or other types of support.

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. The NICE pathway on smoking brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.

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, 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.

Commentary: “This study provides a robust analysis of the risk of neuropsychiatric adverse events associated with varenicline, in the context of people eligible for participation in clinical trials. This backs up the evidence for no association of varenicline with neuropsychiatric events from observational studies.

“However, it should be noted that included trials did vary 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 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 multiple confounding factors, such as the potential neuropsychiatric effects of smoking cessation itself, concomitant medicines, alcohol, and a predisposition to depression. However, 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.

“This short-term rare risk also needs to be balanced with the long-term risks associated with smoking, as well as the risks and effectiveness of other smoking cessation therapies. This study should reassure us that varenicline can be used confidently, as per current NICE guidance. 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). People should be informed in a balanced way about the evidence, but also

encouraged to report any concerns they may have." ***– Dr Anthony Cox, Senior Lecturer in Clinical Pharmacy, University of Birmingham***

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