European Medicines Agency

London, 4 August 2009
Doc.Ref: EMEA/493798/2009

EMEA 2010 Priorities for Drug Safety Research

Suicidal behaviour in relation to certain drug use

Several medicines with different indications and modes of action have been associated with suicidal behaviour including suicidal ideation, attempted and completed suicide. With some of these, confounding by indication complicates attempts to ascertain the relative risk of drug use and risk factors for suicidal behaviour and leads to debate over whether the results are real or due to bias and confounding.

However, suicidal behaviour is a major public health concern not only because of the increased mortality and morbidity in patients, but because of the effects on friends, family and society in general and the associated socioeconomic costs. Therefore any increase in risk – particularly in widely used classes of medicines – is of great public health interest and methodologies are needed to improve both estimation of the risk and early detection of the association.

Atypical and typical antipsychotics have been associated with an increase in the rate of suicide and suicidal behaviour. However, patients with schizophrenia and bipolar disorders – for which these drugs are frequently prescribed - themselves have suicide attempt and completed suicide rates much higher than the general population. The risk is highest soon after diagnosis and so could be associated with the onset of therapy, unhappiness at the diagnosis, fear of further personality disintegration or a combination of the above. Patients with a greater insight into their illness have been found to be at higher risk of suicidal behaviour which could confound the association with treatment.

Use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression has been linked to an increase in suicidal behaviour. The risk is particularly high in the first weeks of treatment but whether this increase is causally related or whether the effect is due to confounding and bias is still the subject of debate.

Montelukast is licensed in the EU for the treatment of mild to moderate asthma in patients inadequately controlled on inhaled steroids and beta-agonists. Montelukast binds to the CysLT receptor preventing leukotriene moderated effects on bronchoconstriction, vascular permeability, mucous secretion and eosinophil recruitment. Reports associating Montelukast treatment and suicidal behaviour have been received by the EMEA. However, allergy itself is thought to increase the risk of depression and suicidal behaviour, possibly through a neurobiological effect of cytokines.

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Varenicline tartrate is a selective partial agonist for α4β2 nicotinic acetyl receptor subtypes and binds to neuronal nicotinic acetylcholine receptors preventing nicotine
binding and producing agonist activity. It was approved in the EU in September 2006 as an aid to smoking cessation. Smoking, smoking therapy and nicotine use are associated with alterations in neurotransmission and smoking cessation has been associated with a deterioration in existing psychiatric conditions. It is unclear whether reports of suicidal behaviour associated with varenicline are causally related to the drug, to smoking cessation or worsening of pre-existing psychiatric illness.

Ascertaining the effect of drugs on the risk of suicidal behaviour poses difficulties. Confounding is a major problem along with the fact that suicidal behaviour is associated with multiple risk factors so failure to measure these accurately may flaw a study.

It is therefore important that methodologies are developed to improve the ability of epidemiological studies to determine any increased risk in suicidal behaviour whilst controlling for potential confounding and measuring any bias. The purpose of required research is the development of a general methodological framework to study the relationship between the use of medicines and suicidal behaviour. The research should also include testing methods in actual epidemiological studies investigating the association of some or all of the drugs described above with such behaviour.