Saskatchewan Drug Information Services
College of Pharmacy and Nutrition, U of S
T:(306)966-6340 F:(306)966-2286
www.druginfo.usask.ca

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Drug Induced Psychiatric Adverse Effects: Depression and Suicide

Chemical influences are capable of producing a myriad of effects on the activity and function of the central nervous system (CNS).[1] Prescription drugs can have adverse effects on mental functioning other than additive sedation, such as psychiatric effects. Psychiatric effects of drugs can impact sensorium, attention, concentration, memory, and higher cognitive functions such as orientation, abstraction, and calculation.[1] Since our knowledge of different regions of brain function and the neurotransmitters in the brain is limited, the explanations for the mechanisms of drug action may be vague. The known neurotransmitters involved are: acetylcholine (memory and learning); norepinephrine (mania-depression and emotions); and serotonin (biological rhythms, sleep, emotion, and pain).[2] Both medical illnesses and medications can cause psychiatric symptoms in vulnerable patients.[2] Generally in regards to psychiatric effects associated with drug therapy, complications such as depression and suicidality (suicidal thinking and behavior) are those most frequently reported. Some prescription drugs with known psychiatric reactions include: steroids, sulphonamides and other anti-bacterials, hormonal drugs, acne drugs, attention-deficit hyperactivity disorder (ADHD) drugs, anti-depressants, anti-parkinsonians, anti-convulsants, anti-malarials, antihypertensives, antihistamines, tranquillizers, statins, and anti-smoking agents.[2] This newsletter will discuss varenicline (Champix®), isotretinoin (Accutane™), and montelukast (Singulair®), which have been getting a lot of attention within the media and the healthcare professional community in regards to the aforementioned side effects.

Varenicline (CHAMPIX®):

There have been post-marketing reports of serious psychiatric adverse events, including depressed mood, agitation, hostility, changes in behavior, suicidal ideation and suicide, as well as worsening of pre-existing psychiatric illness with individuals taking varenicline.[3] A number of confounding factors may have contributed to the serious psychiatric conditions reported in patients taking varenicline. These include the effects of nicotine withdrawal due to partial or complete smoking discontinuation; concomitant, or history of psychiatric conditions; and the concomitant use of other CNS drugs and/or alcohol.[4] It should be taken into consideration, however, that there are cases for which these confounding factors did not appear to be present. Additionally, there have also been other cases where symptoms developed following the cessation of varenicline therapy.[4,5] According to the Food and Drug Administration (FDA), as of March 2008, there were 491 reports of suicidal thoughts and 39 completed suicides out of about 5 million treated patients.[6]

Since the introduction of CHAMPIX in Canada, in April 2007 through April 30, 2008, a total of 226 Canadian cases of neuropsychiatric adverse events have been reported. For the same time period, there have been 708 534 prescriptions filled for CHAMPIX in Canada. [4] It is not clear whether varenicline is to blame, or if nicotine withdrawal or underlying psychiatric disorders play a role.[6]

It is important to note that smoking cessation with or without treatment is associated with various symptoms; dysphoric or depressed mood, insomnia, irritability, frustration, anger or hostility, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite or weight gain have been reported in patients attempting to stop smoking.[7] Such symptoms can potentially manifest into depression.[7] Before taking varenicline, patients should be evaluated for previous or current depression or other mental health problems. Individuals with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder were excluded from the pre-marketing studies of varenicline and thus the safety and efficacy of varenicline in such patients have not been studied.[4] Therefore, patients with psychiatric illness should try other means of smoking cessation initially or be very carefully monitored until further information is available about the effect of varenicline on mental health.

Health Canada is also informing Canadians that it is in the process of further strengthening the labeling for the drug with respect to the risk of serious psychiatric adverse effects.[4] Health Canada is currently working with Pfizer, the manufacturer of *Champix®)*, to update the prescribing information to reflect current safety information. The Canadian Product Monograph for Champix® was first updated in December 2007 and again in May 2008 to reflect important safety information related to the aforementioned serious psychiatric side-effects described.[4] If you suspect that varenicline may not be a product suitable for a particular patient, it may be best to start with a nicotine replacement therapy along with other quit smoking strategies. Encourage behavioral help for patients who use varenicline.[6] Also consider nicotine replacement therapy or bupropion for patients who can't tolerate varenicline.[6]

Isotretinoin (ACCUTANE™):

Acne vulgaris is the most common cutaneous disorder in North America.[8] Patients with acne can experience significant psychological morbidity and, rarely, mortality due to suicide.[8] The psychological effects of embarrassment, anxiety, and shame impact both social lives and employment. Scars can be permanent and a source of self-consciousness.[8] There have been an increasing number of reports which suggest a temporal association between isotretinoin and the occurrence of depression, suicidal ideation and rarely, suicide, in young people.[9] This drug ranks in the top 10 of the FDA's database of drugs associated with reports of depression and suicide attempts.[10, 11] In Canada, of the adverse events reported to Health Canada since the drug was first marketed in 1983, approximately 25% involved psychiatric adverse events, including depression and suicidal ideation.[9] A warning of a possible link with depression and suicide was issued in 2001 by Health Canada.[9, 10]

The majority of patients with severe acne are young. Teenagers and young adults are at increased risk of depression, suicidal ideation and suicide.[12] Both adolescents and acne patients can have significant psychological problems, including depression.[12] It is also thought that severe acne itself may be a risk factor for depression.[11, 13] In some patients, depression has subsided with

discontinuation of therapy and recurred when isotretinoin therapy was re-introduced.[11] Cases showing positive dechallenge and rechallenge are important in pointing to individual susceptibility.[14] Depression that is caused by isotretinoin usually resolves when the isotretinoin is stopped.[15] This does not necessarily prove causation but it does show a worrisome link. It is important to note that successful treatment of acne can also improve quality of life and enhance self-esteem – factors that can lead to improvement in depressive and anxiety symptoms.[8, 16]

Isotretinoin's link to psychiatric adverse events is controversial and a causal relationship has not been definitively established at this time. Depressive disorders are common in the population, and up to 5.6% of patients with mild to moderate acne may have pre-existing suicidal ideations;[10] however, there is biological evidence that retinoids in general can influence the central nervous system (CNS) and in particular neuronal development, neurotransmitters and systems known to be involved in the pathogenesis of psychiatric disorders.[11] All patients should be screened and monitored for signs of depression during therapy, and particular care should be taken in patients with a personal or family history of depression. If symptoms of depression develop or worsen during treatment with isotretinoin, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment as necessary.[9] Most acne can be effectively managed with topical agents, oral antibiotic therapy or oral contraceptive therapy. Isotretinoin should be reserved for more severe, recalcitrant, scarring acne.[10]

Montelukast (SINGULAIR®):

In March 2008, the FDA informed healthcare professionals and patients of the possible association between the use of montelukast with mood changes and suicidality.[17] Montelukast is a leukotriene receptor antagonist used to treat asthma, the symptoms of allergic rhinitis, and to prevent exercise-induced asthma.

The findings from a review of three randomized, double-blind, controlled trials that included montelukast as a treatment assignment to study the effect of montelukast on emotional well being led to the conclusion that the evidence does not suggest this is a general concern, despite what has recently been reported in the media.[18] It is important to acknowledge that despite the strength of having randomized comparison groups in the studies examined, there are certain limitations, such as patients participating in clinical trials may be excluded for significant psychiatric illness and that studies up to 24 weeks cannot exclude the possibility of long-term effects.[19] Although, the review did not find evidence of a negative effect of montelukast on emotional well being, one cannot exclude the possibility of idiosyncratic reactions to montelukast.

After an investigation, the FDA requested the manufacturers of leukotriene antagonists to include information about neuropsychiatric events in the *Precautions* section of the product monographs; updates took effect August, 2009.[19] Currently, Health Canada has not issued any advisories on this matter. The Singulair® monograph includes information regarding neuropsychiatric effects in the Adverse Drug Reactions section, but not in the precautions.[20] As of January 31, 2009, Health Canada has received 42 reports of suicidality and other psychiatric reactions suspected to be secondary to montelukast use. Positive dechallenge was reported in 27 of these cases and positive rechallenge in five.[21]

Overall, the potential link between montelukast use and an increased suicide risk is surprising because there is nothing obvious about montelukast's pharmacology that would link it to psychiatric events.[22] Nonetheless, healthcare professionals and caregivers should monitor patients taking montelukast for suicidality and changes in behavior and mood.[17] Advise patients not to stop these drugs without first talking with their pharmacist or their prescriber.[22]

Final Points for Consideration:

The ability to identify depressive episodes or suicide related to drug therapy in uncontrolled post-marketing surveys can be difficult.[18] Managing marketed health product-related adverse reactions depends on healthcare professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Due to the fact that these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.[3] The US FDA regulatory body has requested that pharmaceutical companies look for signs of suicidal thoughts during drug trials to further add to the current body of knowledge of neuropsychiatric side effects of medications. In addition, clinical trials should include follow up for signs of dependence and specific questions about psychiatric symptoms. An important variable in the production of adverse psychiatric reactions is personal predisposition. The risk is increased in those with pre-existing impairment of brain function, the elderly, past or present psychiatric illness, or a history of alcohol or drug abuse; however, those with unblemished psychiatric records are by no means immune.[2]

In summary, pharmacists should

- Be prepared to discuss patient concerns about media reports to reassure the patient and to ensure that their concerns are addressed appropriately.
- Discourage discontinuation of medications based on media reports unless patients are medically advised to do so.
- Assess patients starting therapy on these medications. Problem identification and therapeutic monitoring cannot occur unless a thorough assessment is first completed to serve as baseline for evaluating response and emerging adverse effects.
- Facilitate ongoing monitoring for adverse effects by the patient, the patient's caregivers and/or healthcare professionals. If recognized quickly, action may be taken to possibly prevent more serious consequences.
- Ensure that adverse affects associated with these medications are reported to Canada Vigilance.

Prepared by Gurpreet Sahi, SPEP Student: Saskatchewan Drug Information Service, Carmen Bell BSP, Drug information Consultant and Karen Jensen MSc, BSP, Drug Information Consultant

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