Serotonin syndrome and smoking cessation medicines

Dear Editor,
Could I please have some clarification regarding the interaction of Zyban and Champix with other antidepressants (SSRIs and venlafaxine in particular)? I am starting to hear reports of serotonin syndrome and ICU admissions.

Dr Amy Kempthorne, GP
Auckland

Bupropion (Zyban) is used as a smoking cessation medicine in New Zealand. It is also used in other countries to treat major depressive order. Bupropion is a dopamine-noradrenaline reuptake inhibitor, which increases the concentrations of noradrenaline (norepinephrine) and dopamine in the body.

Serotonin syndrome occurs when there is excessive serotonergic activity in the body, most often due to concurrent or excessive administration of medicines that affect serotonin levels. The syndrome is characterised by rapid onset of a triad of symptoms that can be life threatening:

- Cognitive: headache, agitation, confusion, hallucinations, coma
- Autonomic: shivering, sweating, hypertension, tachycardia, nausea, diarrhoea
- Somatic: muscle twitching, tremor

Although rare, there have been several reports of bupropion associated serotonin syndrome.[1,2] Bupropion itself has no serotonergic activity,[3] however, it does inhibit hepatic enzyme P450 CYP2D6, the same enzyme that metabolises antidepressants such as fluoxetine, paroxetine, amitriptyline and venlafaxine. This effect may result in elevated serum levels of these antidepressants in individuals who are already poor metabolisers, due to genetic polymorphisms in the CYP2D6 gene, thereby increasing the risk of developing serotonin syndrome.

Regardless of the risk of serotonin syndrome, bupropion should be prescribed with caution to people concurrently taking antidepressants due to the risk of seizures. Bupropion lowers the seizure threshold and is contraindicated in people with seizure disorders, eating disorders, those withdrawing from alcohol or benzodiazepines and people taking monoamine oxidase inhibitors. Extreme caution is advised when patients are concurrently taking other medicines which lower the seizure threshold such as antidepressants, antipsychotics, insulin or other hypoglycaemic agents, sedating antihistamines, anorectics, tramadol, systemic steroids and quinolones.[4]

Varenicline (Champix) is a smoking cessation medicine which acts as a partial agonist of the nicotinic acetylcholine receptor. This medicine is not an antidepressant and it has no serotonergic activity. Varenicline is not significantly metabolised and is largely excreted in the urine. Since varenicline does not affect the cytochrome P450 CYP pathway, it is unable to increase serotonin levels by influencing metabolism of antidepressant medicines.[5] It is unlikely that varenicline has any effect on serotonin release, or reuptake, and there are no published reports of varenicline induced serotonin syndrome.

Some patients using varenicline have reported adverse effects including depression and suicidal thoughts, and use may exacerbate underlying psychiatric conditions. Care should be taken when prescribing varenicline to patients with a history of mental illness, even if they are not currently being treated. Patients should be advised of this risk and the need to report any symptoms. Varenicline is currently being monitored by the Intensive Medicines Monitoring Programme (IMMP) and more information about its adverse effects may become available in the future.

For further information see: "Smoking cessation – pharmacological therapy", BPJ 20 (Apr, 2009)

"Snippets: Suicidal thoughts and behaviours associated with varenicline use", BPJ 13 (May 2008).

References

1. Munhoz R. Serotonin syndrome induced by a combination of bupropion and SSRIs. Clin Neuropharmacol 2004;27(5):219-22.
2. Thorpe E, Pizon A, Lynch M, Boyer, J. Bupropion induced serotonin syndrome: a case report. J Med Toxicol 2010;6:168-71.
3. Gillman P. Bupropion, bayesian logic and serotonin toxicity. J Med Toxicol 2010;6:276-7.
4. GlaxoSmithKline. Zyban. Medicine Datasheet. 2010. Available from: www.medsafe.govt.nz (Accessed May, 2011).
5. Faessel H, Obach R, Rollema H, et al. A review of the clinical pharmacokinetics and pharmacodynamics of varenicline for smoking cessation. Clin Pharmacokinet 2010;49(12):799-816.

The evidence for breast screening

Dear Editor,

I enjoyed reading your article "Increasing the uptake of breast screening", BPJ 33 (Feb, 2011). Many general practices spend considerable time, effort and money attempting to do just that. Much of that effort takes the form of personalised invitations and face to face attempts at persuading women, who are often rather sceptical of the prospect of undergoing a sometimes uncomfortable procedure. We owe it to these women to ensure that we have our facts straight and can deliver them in an understandable way.

A good start is ensuring that all are in agreement that mammography does not prevent breast cancer. This point is made quite clearly at the start of the article but is worth repeating as misleading slip-ups can occur when a message is being repeated on many occasions to different people. Later in the article the authors fall prey to this error themselves when they incorrectly suggest that women with a breast cancer gene can "...reduce their risk of developing breast cancer with options including more frequent screening and starting (mammography) at a younger age".

*We do know that mammograms can detect a breast cancer before it is symptomatic, although this in itself does not mean that the person will survive the breast cancer. This is where the statistics can begin to deceive. The authors state the relative risk reduction (of death from breast cancer) for woman undergoing regular mammography as 25% to 30%. If a thousand women are screened with mammograms for ten years two will die from breast cancer instead of three (the figure for the unscreened population). A general practice of say 2000 patients might have 350 eligible women and would need to run a 100% uptake rate mammogram programme with no drop-outs for thirty years to prevent one of these women from dying from breast cancer. Because abnormal results are quite frequent, and 90% of those are false positives, by the time these woman have completed all their free mammograms half of them will have had one or more positive results and undergone further investigation to discover that they do not have breast cancer.**

* *Elmore J, Barton M, Moceri V, E=et al. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 1998; 338(16):1089-96.*

My point is not to attempt to address the good versus harm debate, but simply to ask if women are being given the opportunity to make an informed decision for themselves? The most informative of Breastscreen Aotearoa's various multilingual information leaflets (HE1801) mentions the existence of false negatives and false positives but quotes no figures at all in terms of either relative or absolute risk reduction. It, therefore, falls to clinical staff to answer patient's questions and we better be sure we have our facts right.

Dr Kerr Wright, GP
Auckland

To allow women to make informed decisions about breast screening, general practitioners and practice nurses need to be able to discuss with their patients the pros and cons of screening and to understand how New Zealand guidelines are arrived at.

The aim of any cancer screening programme is to ensure that nobody with cancer goes undetected. As a result, some people will be called back for a secondary examination due to suspicious or indeterminate results, but in the majority of cases, cancer is not confirmed in these patients, i.e. a false positive. The harm (i.e. anxiety) associated with false positive results needs to be weighed up with the benefits of screening.

The National Screening Unit recommendations aim to reduce the amount of breast cancer false positives by targeting women in the age range of 45 to 69 years with biannual breast screening, because:

- Breast cancer rates are significantly elevated in this age group
- Biannual testing provides 70 to 99% of the benefits of annual testing[1]

Screening more frequently, or screening of a wider cohort is not performed because:

- Detection of breast cancer by mammogram is more difficult in younger women due to denser tissue and false positives are more common
- Annual testing significantly increases the number of false positives[2]

It is generally accepted that the relative risk reduction for international breast screening programmes with a 70% participation rate is 20–30%.[3, 4] What makes the relative risk reduction meaningful is the incidence of breast cancer. Each year approximately 2300 New Zealand women develop breast cancer and 630 will die from it. This makes breast cancer the leading cause of cancer death for women aged 45 to 69.[5] Applying a 25% risk reduction to a New Zealand setting means that if no screening were to occur at all, then each year approximately 840 women would die, i.e. 210 more than if screening did occur.

The absolute risk reduction is calculated by determining the risk of dying from breast cancer and applying the relative risk reduction to this figure, if breast screening occurs. For example, if the risk of dying from breast cancer in a 60 year old woman in the next ten years was 9 in 1000, then screening would reduce this risk by 20–30%. This means that a woman in this age group now has a 6 to 7 in 1000 chance of dying from breast cancer if she has biannual breast screening. As the absolute risk of dying from breast cancer decreases with age, younger women derive less benefit from the relative risk reduction achieved from breast screening.

However, perhaps a more important statistic is the number of women that need to be screened to prevent one death. A meta-analysis, published in the United States, of six trials among women aged 50 to 59 years and two trials among women aged 60 to 69, calculated that the number of women needed to be screened by mammography, every two years, to prevent one death, was 1339.[1] In New Zealand, the uptake of breast screening among eligible women (i.e. aged 45 to 69 years) is approximately 67%,[6] equating to over 450 000 women screened every two years.

Although the New Zealand breast screening programme undoubtedly prevents deaths, the trade off is the anxiety of false positives and the discomfort and potential pain of the procedures required for screening and investigation. Through informed discussion with their GP and practice nurse, every woman should have the right to make her own decision on whether she undergoes breast screening.

N.B. The correspondent is correct in stating that mammography does not prevent breast cancer from occurring, it enables detection of tumours that can then be treated to prevent the cancer developing and therefore to reduce the risk of death. Mammography does not

detect all tumours and the two year interval between screening means that some fast-growing tumours, which are associated with a higher risk of mortality, may not be detected.

We value your feedback. Write to us at: Correspondence, PO Box 6032, Dunedin or email: editor@bpac.org.nz

References

1. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;151(10):716-26.

2. Elmore JG, MB B, Moceri VM, et al. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 1998;338(16):1089-96.

3. Gummersbach E, Piccoliori G, Zerbe CO, et al. Are women getting relevant information about mammography screening for an informed consent: a critical appraisal of information brochures used for screening invitation in Germany, Italy, Spain and France. Eur J Pub Health 2009;20(4):409-14.

4. Nelson H, Tyne K, Naik A, et al. Screening for breast cancer: systematic evidence review update for the U.S. Preventive Services Task Force. US Preventative Services Task Force Evidence Syntheses. Rockville (MD), USA: Agency for Healthcare Research and Quality, 2009. Available from: www.ncbi.nlm.nih.gov/books/NBK36391/#ch4.s1 (Accessed May, 2011).

5. Ministry of Health. Cancer: New registrations and deaths 2007. In: Ministry of Health, editor. Wellington: Available from: www.dhbnz.org.nz (Accessed May 2011), 2010.

6. DHBNZ. National summary of PHO Performance 1 January 2010 - 30 June 2010. Wellington: DHBNZ, 2010. Available from: www.dhbnz.org.nz (Accessed May, 2011).