European Neuropsychopharmacology (2012) **22**, 841–843

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EDITORIAL

On assessing potential efficacy for vortioxetine in generalized anxiety disorder

There is much room for improvement in the pharmacological treatment of patients with generalized anxiety disorder. The 'ideal' drug would have a rapid onset of effect, be beneficial in reducing psychological and physical symptoms of anxiety, across the range of severity, and be effective in achieving symptom remission. It would be suitable for once-daily dosage, have limited adverse effects, cause negligible interference in daily life, be free from drug interactions, and suitable for use in physically ill patients. Over long-term treatment, it would be effective in preventing relapse, and neither associated with development of tolerance during continuing use, nor with discontinuation symptoms once stopped (Baldwin et al., 2011). Sadly, although many drugs are efficacious and licensed for treating generalized anxiety disorder, the 'ideal' drug is not yet available. Response rates are often disappointing, many patients experience unwanted effects, others will relapse despite continued adherence; and discontinuation symptoms can be troublesome. Hence there is considerable scope for developing novel treatments with enhanced effectiveness and greater acceptability, when compared with existing medications (Baldwin, 2011).

The novel psychotropic drug vortioxetine (previously LuAA21004, H. Lundbeck A/S) is a multimodal antidepressant with a complex mechanism of action which includes inhibition of the 5-HT transporter protein, antagonist effects at 5-HT_3 and 5-HT_7 receptors, and agonist effects at the 5-HT_{1A} receptor (full) and 5-HT_{1B} receptor (partial). The net effect of this pharmacology is that it increases levels of 5-HT, noradrenaline, dopamine, acetylcholine and histamine in ventral hippocampus and medial prefrontal cortex (Bang-Andersen et al., 2011). This pharmacological profile, and the findings from animal models, together suggest the potential for efficacy in treating patients with major depressive disorder or generalized anxiety disorder. An initial randomised placebo-controlled venlafaxine-referenced trial found it to be efficacious in reducing both depressive and anxiety symptoms in depressed patients (Alvarez et al., 2012).

So far, so good. Unfortunately, subsequent studies have produced inconsistent findings. There is good evidence for vortioxetine in relapse prevention, in both major depressive disorder (Boulenger et al., 2012) and generalized anxiety disorder (Baldwin et al., 2012a), and further support for efficacy in the acute treatment of depression (Henigsberg et al., 2011; Katona et al., 2012): though a 'failed' trial (Baldwin et al., 2012b)—in which duloxetine was also not significantly superior to placebo on the primary outcome measure—found only evidence supportive of likely antidepressant efficacy for vortioxetine. A further study in patients with major depression found that vortioxetine did not differ significantly from placebo (Jain et al., 2011) and recent randomised placebo-controlled trials of the acute treatment of generalized anxiety disorder, included within this issue of *European Neuropsychopharmacology*, have also produced inconsistent results (Bidzan et al., in press; Rothschild et al., in press): so how should we interpret this range of findings?

Demonstrating efficacy within acute treatment studies in patients with major depressive disorder or generalized anxiety disorder is not easy. Less than 50% of clinical trials with anxiolytic drugs approved by the United States Food and Drug Administration found evidence of statistical superiority to placebo (Khan et al., 2002), and approximately half of randomised controlled trials with antidepressants have not found efficacy in at least one treatment arm (Khin et al., 2011). Furthermore, the best method of statistical analysis for assessing potential efficacy within randomized placebo-controlled trials is the subject of some debate: with arguments for both the more conservative last observation carried forward (LOCF) approach favoured by regulatory bodies, and for the more forgiving mixed model for repeated measures (MMRM) approach, favoured by some biostatisticians (see for example, Lane, 2008; Siddiqui et al., 2009; Burzykowski et al., 2010). By way of illustration, the 'failed' study of vortioxetine, which employed the LOCF approach to assessing change from baseline to endpoint in the primary outcome measure, would have found evidence for efficacy for duloxetine and two fixed daily doses (5 mg and 10 mg) of vortioxetine if the MMRM approach had been used instead (Baldwin et al., 2012b).

0924-977X/$ - see front matter
http://dx.doi.org/10.1016/j.euroneuro.2012.07.018

Given these uncertainties, it seems reasonable to anticipate that not all findings from the pool of randomized controlled trials with a putative new antidepressant or anxiolytic drug would be consistent.

Although the two studies had a similar design, there were subtle differences in the nature of the participating patients, which might underlie the differences in results. Baseline symptom severity was lower, and the duration of symptoms was longer, and body mass index higher, in the trial conducted in the United States (Rothschild et al., in press); but there was a greater proportion of participants in the 'European' study (which included some patients recruited in South Africa) who had undergone previous treatment, and treatment with medication, for generalized anxiety disorder (Bidzan et al., in press). Lower symptom severity, longer symptom duration, and previous non-response may all be important factors in identifying a patient sub-group which is less likely to benefit from treatment (Baldwin et al., 2011). A greater proportion of participants became 'lost to follow-up' in the United States study, potentially causing a reduced ability to detect significant differences between treatments. The influence of these demographic and clinical factors, and variations in the methods used for patient recruitment, could be explored as the vortioxetine clinical trial database expands, to identify patient sub-groups which are more likely to benefit.

An intriguing finding, seen in both trials, is the occurrence of nausea as a 'treatment emergent adverse event' (European study: placebo, 6.0%, vortioxetine, 12.0%; United States study: placebo, 4.6%, vortioxetine, 25.0%), as the 5-HT_3 antagonist properties of vortioxetine were predicted to confer some protection against nausea. Selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment is not infrequently accompanied by nausea—for example, it had an incidence of 33.5% with the comparator drug duloxetine in the dose-finding study of vortioxetine in major depression (Baldwin et al., 2012b), but investigation of the mechanisms underlying nausea, and assessment of its intensity and duration during vortioxetine treatment would be beneficial. By contrast, reports of sexual dysfunction as a treatment emergent adverse event were infrequent with vortioxetine (less than 5%) in both trials, suggesting that more detailed investigation of sexual functioning during vortioxetine treatment may be worthwhile.

Neither trial included an assessment of the effects of double-blind treatment on measures of cognitive performance. The 5-HT_7 receptor may mediate attentional and memory processes relevant to novelty-induced arousal (Ballaz et al., 2007), and further exploration of the effects of vortioxetine on cognitive performance should be undertaken both in healthy volunteers, and in patients with generalized anxiety disorder: particularly as it showed superiority to placebo in tests of speed of processing, verbal learning and memory, in elderly depressed patients (Katona et al., 2012).

Role of the funding source

No funding was sought or obtained in connection with this editorial.

Contributors

David Baldwin and David Nutt contributed similarly to the writing of this editorial.

Conflict of interest

On behalf of his employer, DSB received consulting fees for planning and supervising two randomized controlled trials with Lu AA21004, and personal support for travel to study-related meetings. He has received honoraria for educational presentations from H. Lundbeck A/S, Pfizer and Servier, and has acted as a paid consultant to Eli Lilly, Grunenthal, Lundbeck and Pfizer, and currently holds research grants (on behalf of his employer) from Lundbeck and Pfizer. He has accepted paid speaking engagements in industry-supported satellite symposia or other meetings hosted by Eli Lilly, Lundbeck, Pfizer and Servier. DJN acts as a scientific consultant for Lundbeck, Servier, Reckitt-Benkiser, Lilly and BMS. He has received speaking honoraria from these and also Otsuka and D&A pharmaceuticals.

References

Alvarez, E., Perez, V., Dragheim, M., Loft, H., Artigas, F., 2012. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in subjects with major depressive disorder. Int. J. Neuropsychopharmacol. 15, 589–600.

Baldwin, D.S., Waldman, S., Allgulander, C., 2011. Evidence-based pharmacological treatment of generalized anxiety disorder. Int. J. Neuropsychopharmacol. 14, 697–710.

Baldwin, D.S., 2011. Where is the room for improvement in the drug treatment of depression and anxiety? Hum. Psychopharmacol. 26, 1–3.

Baldwin, D.S., Loft, H., Florea, I., 2012a. Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. Int. Clin. Psychopharmacol. 27, 197–207.

Baldwin, D.S., Loft, H., Dragheim, M., 2012b. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of LuAA21004 in acute treatment of major depressive disorder (MDD). Eur. Neuropsychopharmacol. 22, 482–491.

Ballaz, S.J., Akil, H., Watson, S.J., 2007. The 5-HT7 receptor: role in novel object discriminationand relation to novelty-seeking behaviour. Neuroscience 149, 192–202.

Bang-Andersen, B., Ruhland, T., Jorgensen, M., Smith, G., Frederiksen, K., Jensen, K.G., 2011. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a multimodal compound for the treatment of major depressive disorder. J. Med. Chem. 54, 3206–3321.

Bidzan, L., Mahableshwarkar, A.R., Jacobsen, P., Yan, M., Sheehan, D.V. Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. Eur. Neuropsychopharmacol, http://dx.doi.org/10.1016/j.euroneuro.2012.07.012, in press.

Boulenger, J-.P., Loft, H., Florea, I., 2012. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. J. Psychopharmacol. (E-pub ahead of print).

Burzykowski, T., Carpenter, J., Coens, C., Evans, D., France, L., et al., 2010. Missing data: discussion points from the PSI missing data expert group. Pharm. Statist. 9, 288–297.

Henigsberg, N., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y., Thase, M.E., 2011. Efficacy and safety of multiple doses of Lu AA21004 in an 8-week treatment of adults with major depressive disorder. Eur. Neuropsychopharmacol. 21 (Suppl. 3), S393.

Jain, R., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y., Thase, M.E., 2011. Efficacy and tolerability of Lu AA21004 5 mg in a 6-week treatment of adults with major depressive disorder. Poster Presentation, Annual Meeting of the American Psychiatric Association, Honolulu, Hawaii, USA, May 14–18, 2011.

Katona, C., Hansen, T., Olsen, C.K., 2012. A randomized, double-blind, placebo-controlled, duloxetine-reference, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. Int. Clin. Psychopharmacol. 27, 215–223.

Khan, A., Khan, S., Brown, W.A., 2002. Are placebo controls necessary to test new antidepressants and anxiolytics? Int. J. Neuropsychopharmacol. 5, 193–197.

Khin, N.A., Chen, Y.-F., Yang, Y., Yang, P., Laughren, T.P., 2011. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J. Clin. Psychiatry 72, 464–472.

Lane, P., 2008. Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches. Pharm. Stat. 7, 93–106.

Rothschild, A.J., Mahableshwarkar, A.R., Jacobsen, P., Yan, M., Sheehan, D.V. Vortioxetine (Lu AA21004) 5mgingeneralized anxiety disorder: results of an 8-week, randomized, double-blind, placebo-controlled clinical trial in the United States. Eur. Neuropsychopharmacol, http://dx.doi.org/10.1016/j.euroneuro.2012.07.011, in press.

Siddiqui, O., Hung, H.M., O'Neill, R., 2009. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J. Biopharm. Stat. 19, 227–246.

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21 July 2012

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