

Mirtazapine-induced akathisia

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TO THE EDITOR: Akathisia is a clinical syndrome that manifests as the subjective sense of unease or restlessness, or observable motor manifestations such as shuffling or tramping movements of the legs and feet, or both.¹ The marked distress associated with akathisia can lead to impulsive suicide attempts.² It is commonly associated with antipsychotic medications, as well as various antidepressants, including tricyclics and selective serotonin reuptake inhibitors (SSRIs).

Mirtazapine is a novel antidepressant. It acts centrally to increase both noradrenergic and serotonergic neurotransmission. Common side effects include sedation, weight gain and increased appetite. Tremor is listed as an adverse reaction, but this does not represent akathisia. A MEDLINE database search (up to September 2001), using the words "akathisia" and "mirtazapine", did not reveal any reports of an association. However, as of mid-November 2001, the Adverse Drug Reactions Advisory Committee (ADRAC) had received five reports of "hyperkinesia (probably equivalent to akathisia)" associated with mirtazapine.

We would like to report two cases of acute akathisia associated with mirtazapine.

A 52-year-old man was referred by his psychiatrist for inpatient management of his depressive illness. He had previously tried multiple antidepressants, including various tricyclics and SSRIs. However, because of the sexual side effect anorgasmia, adherence to antidepressant treatment was poor. He was prescribed mirtazapine (30 mg at night). Within an hour of taking the first dose, he complained of feeling restless and unable to keep his legs still. He was given 1 mg of clonazepam, which settled his symptoms after 30 minutes. He was also observed to jiggle his legs and feet while at rest. His symptoms recurred the next day, necessitating further successful treatment with clonazepam. Mirtazapine therapy was continued, and the patient's depression improved significantly over the next few days, and the akathisia gradually resolved with regular use of clonazepam.

A 73-year-old woman with chronic depression was admitted after an overdose. Her medications on admission were omeprazole, amiodarone, bendrofluzide and fluvoxamine (50 mg). The fluvoxamine was

changed to mirtazapine (15 mg/day initially, increased to 30 mg/day after three days). After the first 30 mg dose, she described intense restlessness in her legs lasting up to two hours. The distress necessitated reintroducing the fluvoxamine in place of the mirtazapine. Within three weeks the patient was readmitted with depressed mood and suicidal ideation. Mirtazapine (30 mg at night) was reintroduced, with consequent acute return of restless legs. The patient's akathisia settled when the mirtazapine was reduced to 15 mg at night. No additional treatment was required.

The neurobiological basis for akathisia remains unclear. Involvement of central serotonergic and adrenergic neurotransmitter systems has been postulated. One of mirtazapine's main actions is blockade of α_2 -adrenoreceptors. Clonidine, an α_2 -agonist, is effective in treating akathisia.³ We suggest that mirtazapine's adrenoceptor action might be the basis for the occurrence of akathisia in these patients.

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Vitamin D deficiency and multicultural Australia

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TO THE EDITOR: In a recent editorial, Mason and Diamond state that ergocalciferol (vitamin D₂) is bioequivalent to cholecalciferol (vitamin D₃) and that 1000 IU/day of ergocalciferol is sufficient for the treatment of vitamin D deficiency.¹ Both statements are contentious. Although ergocalciferol (vitamin D₂) is the only single prohormonal form of vitamin D available on prescription in Australia, there are three reasons to be cautious about the use and dose equivalence of ergocalciferol (vitamin D₂) compared with cholecalciferol (vitamin D₃).

Cholecalciferol (and not ergocalciferol) has been shown in two randomised trials to reduce fracture rates when administered concomitantly with calcium to elderly patients.^{2,3} Furthermore, all recently studied agents for treating postmenopausal osteoporosis (alendronate, risedronate, raloxifene and parathyroid hormone 1-34 [the first 34 amino acids of the hormone])

were shown to lower fracture rates, but study participants were routinely given supplementary calcium and vitamin D when deficiency was established. At least two studies specified the use of cholecalciferol.

Vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol) are probably not bioequivalent.^{4,5} Ergocalciferol administration to vitamin-D-replete premenopausal women reduced the amount of circulating 25-hydroxyvitamin D₃ (25OHD₃) while only modestly increasing 25OHD₂ levels, with a resultant marginal effect on the total 25OHD level.⁴ In contrast, the equivalent dose of cholecalciferol increased the circulating level of 25OHD₃ significantly.⁴

Lastly, while radioimmunoassays (RIAs), such as the INCSTAR/DioSorin assay (Stillwater, Minnesota, USA), used in both studies of vitamin D levels published recently in the *MJA*^{6,7} are able to measure 25OHD levels, they are incapable of differentiating between 25OHD₂ and 25OHD₃. Furthermore, neither of the commercially available RIAs (the other one is made by IDS Ltd, Tyne and Wear, UK) is able to measure both vitamin D metabolites with equivalent accuracy. In a study comparing RIAs for the measurement of 25OHD against high performance liquid chromatography (the gold standard method) both assays did not recognise 25OHD₂ as well as 25OHD₃, with r^2 of 0.74 and 0.58, respectively, for 25OHD₂.⁸ Until further research is available, using more patients and a greater number with vitamin D deficiency, caution must be exercised in the interpretation of 25OHD levels measured with RIAs. This applies especially to individuals taking ergocalciferol (vitamin D₂) for the treatment of vitamin D deficiency.

Thus, it would appear that cholecalciferol (vitamin D₃) has a role to play in the reduction of osteoporotic fractures, but only when administered with calcium. If administering ergocalciferol (vitamin D₂), a far greater dose than 1000 IU/day may be needed, and the use of commercial RIAs to determine the therapeutic response may be misleading.

Competing interests: None declared.

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IN REPLY: Glendenning raises a number of interesting points, which require some clarification.

Are ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) biologically equivalent?

The statement that ergocalciferol and cholecalciferol are bioequivalent in humans is made by most authoritative textbooks, based mainly on evidence from early studies of the antirachitic efficacy of ergocalciferol and cholecalciferol compounds, and contrasts with reduced efficacy of ergocalciferol in birds and monkeys.¹ Recent studies using more precise measurements have raised some doubts as to the absolute equivalency of ergo- and cholecalciferol, but the differences are marginal² and not universally found.³ There are few recent data on relevant biological endpoints. Serum concentrations of the active hormone, 1,25-dihydroxyvitamin D, were not different after administration of ergo- or cholecalciferol,² and increases in bone mineral density were greater after ergocalciferol therapy than after cholecalciferol in patients taking anticonvulsants.¹ In short, on current evidence, differences in biological activity between ergocalciferol and cholecalciferol are likely to be relatively minor.

Are there problems monitoring therapy?

25-Hydroxyvitamin D values may be used for monitoring treatment. The possibilities of impaired detection of the 25-hydroxy metabolite of ergocalciferol by some assays,² and perhaps a smaller rise in total 25-hydroxyvitamin D concentrations after low doses of ergocalciferol, should be borne in mind when monitoring therapy.

What is the current recommendation for vitamin D supplementation?

While the availability of larger dose sizes and/or cholecalciferol preparations would be helpful, 800 IU of ergocalciferol and 1 g of calcium for six months was shown to reduce secondary hyperparathyroidism in older patients,¹ and 600 IU/day (same for

ergo- and cholecalciferol) is the new recommended adequate intake for older patients with limited sun exposure.¹

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Confronting conflict of interest in research organisations: time for national action

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TO THE EDITOR: A recent editorial in the *Journal* focused on the "blurring of research ideals and corporate interests".¹ But there are other funding and commissioning bodies, including government, whose wants or needs also have the potential to blur research ideals and exert control over what can be published. In recent times, those who pay the piper increasingly want to call the tune. Understandably, this is also an issue for research into Aboriginal ill health.^{2,3} Van Der Weyden's plea for the development of national guidelines on institutional conflict of interest should therefore be broadened to include all funding bodies.

One suggestion for inclusion in these guidelines, to enhance public interest in research, is an obligation for authors to state not only their sources of funding, but "the origin of the research question they are attempting to answer"⁴ and the person or group who initiated the funding of the project.

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Recent appearance of clindamycin resistance in community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in south-east Queensland

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TO THE EDITOR: We report the appearance of erythromycin and inducible clindamycin resistance in the south-west Pacific strain of non-multiresistant methicillin-resistant *Staphylococcus aureus*, which has recently appeared in eastern Australia. Infections occur predominantly in Polynesian people and are usually community-acquired. Most strains belong to Western Samoan phage patterns (WSPP1 or WSPP2) and pulso-type A when typed by pulsed-field gel electrophoresis.^{1,2} These strains are resistant to all β -lactams, but are usually susceptible to erythromycin, clindamycin, gentamicin, tetracycline, trimethoprim-sulfamethoxazole and ciprofloxacin. Although most of these antibiotics would not be recommended for therapy,³ clindamycin has been recommended for non-parenteral treatment of soft-tissue and bone infections, as it is efficacious in treating similar infections caused by methicillin-susceptible *S. aureus*.⁴

Twenty isolates of community-acquired, non-multiresistant pulso-type A MRSA were collected from patients from southern Brisbane and Logan in 1997 and 1998.² A further 16 isolates were obtained from Ipswich patients between December 1998 and February 2001. We found that all 36



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isolates were susceptible *in vitro* to gentamicin, tetracycline, trimethoprim-sulfamethoxazole, ciprofloxacin, rifampicin, fusidic acid and vancomycin. However, two of the Ipswich isolates had erythromycin and inducible clindamycin resistance. When susceptibility testing was performed using standard disc methods, both isolates appeared resistant to erythromycin but susceptible to clindamycin. However, on testing for inducible macrolide resistance (MLSB phenotype) using a disc-approximation method, both showed inducible clindamycin resistance.⁵ These isolates were from superficial abscesses in Polynesian people with community-acquired infection. They were indistinguishable by pulsed-field gel electrophoresis, but there were no epidemiological links. As yet, we have found no community-acquired pulsed-field gel electrophoresis type A strains of MRSA with erythromycin resistance and constitutive (ie, non-inducible) clindamycin resistance.

Two other recent Australian studies found erythromycin resistance in 13 of 153 and three of 29 isolates of non-multiresistant MRSA, respectively.^{3,6} These studies did not report clindamycin susceptibilities, and it was not clear what proportion of the isolates belonged to phage patterns WSPP1 or WSPP2, or were community-acquired.

As clindamycin has been recommended as a therapeutic option for soft-tissue and bone infections caused by non-multiresistant MRSA, this finding of inducible clindamycin resistance has important implications. Microbiology laboratories should screen for inducible clindamycin resistance in erythromycin-resistant strains, and, if found, an alternative antibiotic should be used for treatment.⁷ Alternatively, rather than assessing inducible clindamycin resistance with a disc-approximation test, some laboratories may prefer to report all erythromycin-resistant strains as clindamycin-resistant. Also, given the increasing incidence of community-acquired MRSA infection in Australia, all suspected staphylococcal infections that are not responding to empiric therapy with β -lactam antibiotics should be swabbed for culture.

Acknowledgement: We thank the Ipswich Hospital Foundation for financial support.

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Time for a grant category for curiosity-based research

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TO THE EDITOR: We strongly support the proposal¹ that it is time to create a special grant category for curiosity-based research proposals. Having been in biomedical research for over 50 years, we have experienced a period when most research was curiosity based. We can thus compare with the present situation — research aiming for a rapid, practical and commercial outcome has become almost a necessity for survival because of the increasingly severe reduction in government funding for universities and research institutes. We would like to illustrate the value of curiosity-based research with a few Australian examples from our own fields.

In 1946, one of us (F F) was working on the experimental epidemiology of the causative agent of infectious ectromelia of mice (related to vaccinia virus). A chance observation — that the mice which survived the infection developed a skin rash — led to further study of the virus as a model for smallpox, measles and chickenpox infections. Thus, unexpected discoveries were made about the way the virus spreads through the body during the incubation period of these diseases.²

In 1951, myxomatosis spread in rabbits in the Murray-Darling basin of south-eastern Australia. The virus was initially extremely virulent (99% fatal), but the rabbits slowly developed genetic resistance. One of us (F F) studied the virus for 15 years, and this work was acknowledged as the best example of the co-evolution of viral virulence and host resistance.³

In 1957, Macfarlane Burnet proposed the clonal selection theory of antibody formation — that individual B lymphocytes made antibody of a single specificity.⁴ This was one of the most original concepts ever proposed in biology and it took 10 years to be widely accepted. It has since led to the production of monoclonal antibodies,

which are used as basic reagents in research and diagnostic laboratories, and are now being used in immunotherapy.

In the 1970s, Peter Doherty and Rolf Zinkernagel studied the role of the newly discovered cytotoxic T cells (which could lyse virus-infected cells) to find out how T cells recognised the infected cells. They showed that killing was restricted by the major histocompatibility complex (MHC) and that its role was to signal “altered self” to the T cell.⁵ These studies led to the award of the Nobel Prize in 1996. Cytotoxic T cell activity has since been shown to be the main immune mechanism for controlling and clearing many intracellular infections. Induction of a strong cytotoxic T cell response is the mechanism of candidate vaccines currently being trialled against HIV-1.

In the late 1960s, one of us (G A), together with Chris Parish, showed that a bacterial protein, flagellin, induced antibody tolerance over a wide dose range. Parish was the first to show the inverse relationship between antibody and cell-mediated immune responses, which led others to describe two classes of helper T lymphocytes.⁶ These have been shown to be important in the development of allergy in infants, and offer the opportunity for immunotherapy to reduce the later incidence of allergy.

None of these research programs was initiated with a commercial goal in mind. Benjamin Franklin, when asked about the importance of some research, replied “Of what use is a baby?”.

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