Off-label use of quetiapine in New Zealand—a cause for concern?

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Off-label prescribing is common in psychiatry and often reflects a pragmatic clinical approach to managing refractory symptoms in complex patients. Although often not supported by clinical trial data sufficient to gain regulatory approval for use, there will be supporting data in the form of open trials, case reports, or case series. For rare or treatment-resistant patients, formal controlled clinical trials may not be feasible. Furthermore, some authors have seen off-label usage as important in discovering new indications.1

In this issue, Monasterio and McKean2 have presented survey data from a cohort of Canterbury psychiatrists on frequency and reasons for off-label use of atypical antipsychotic drugs (AAPs). Their main finding is that survey respondents commonly report off-label use of AAPs, and this is almost entirely accounted for by use of quetiapine, for a range of symptoms/indications. Focussing on quetiapine, the drug most commonly identified as being used off-label, how should their findings be interpreted?

The data presented are difficult to evaluate because of study design issues. In contrast to an earlier study3 that examined off-label quetiapine use, the Canterbury study is impressionistic rather than quantitative, and does not collect data on dose, frequency of administration, and patient location (e.g. in- vs out-patient). It is also not clear whether the authors provided a checklist of possible symptoms/indications or these were derived from the responses of survey respondents. These data are important to understand patterns of quetiapine use. For example, in an earlier off-label use survey,3 the majority of patients receiving off-label quetiapine were dosed on an as-needed basis, with 80% receiving doses of 25–50 mg, for agitation, anxiety and insomnia. Such information is important to interpret the significance of the Canterbury survey findings.

In the Canterbury survey, the three most common symptoms/indications for off-label quetiapine included anxiety, sedation, and post-traumatic stress disorder (PTSD), and are discussed further below. The next most frequent symptoms/indications for which quetiapine is reported to be used are of some concern, in terms of a lack of evidence base (e.g. augmentation of another antipsychotic) or potential for harm to patients (e.g. treatment of symptoms of dementia).

Focussing on the most common reported reasons for off-label use (anxiety and insomnia), we disagree with the authors’ unduly negative assessment of the quality of published data to support any of these uses. Effects of quetiapine on Hamilton Anxiety Scale scores and individual anxiety scale items in depressed patients with comorbid anxiety are indicative of a broad anxiolytic action with a rapid onset of effect.4
Other reviews on the efficacy of quetiapine in generalized anxiety disorder (GAD) are positive,\textsuperscript{4,5} as was a recent FDA assessment of efficacy endpoints.\textsuperscript{6} Studies demonstrating efficacy in anxiety disorders besides GAD (e.g. PTSD) are also positive, however data are more limited.\textsuperscript{8} The effects of quetiapine on sleep have been studied using polysomnography, and increases in total sleep time and sleep efficiency have been reported in primary insomnia\textsuperscript{7} and mixed insomnias,\textsuperscript{8} with no evidence of tolerance development. The rapid onset of sedative and anxiolytic effects is consistent with quetiapine’s antihistaminic and antiadrenergic pharmacology.\textsuperscript{4}

If quetiapine were not to be used off-label for anxiety and insomnia, the range of alternative approved anxiolytics and hypnotics in New Zealand is limited. For anxiety, the only approved drugs with a rapid onset of action are benzodiazepines. Sedating antidepressants, older sedating antihistamines and antiadrenergic drugs (e.g. clonidine, prazosin) are also available but not approved for this symptom/indication. (Non-sedating antidepressants and buspirone are effective anxiolytics, however with a much slower onset of action). For insomnia, only benzodiazepines and zopiclone are approved (sedating antihistamines and antidepressants are also available however their use would also be off-label).

If doctors decide to use quetiapine off-label for symptoms of anxiety or insomnia, what are the risks? The most common side effects appear to be metabolic, and occur even at relatively low daily doses.\textsuperscript{9} Other safety issues include a dose-related increase in sudden cardiac death rate in the short term,\textsuperscript{10} and tardive dyskinesia with long-term usage. Concerns about longer-term safety risks were influential in quetiapine’s non-approval for anxiety and depression indications at a recent FDA advisory panel.\textsuperscript{11} However concerns were not raised about short-term or intermittent use with regard to these indications.

Abuse potential has also been identified, however most reports appear to be in forensic settings, in polysubstance abusers.\textsuperscript{12} In relative terms, abuse and dependence liability appears to be much greater for benzodiazepines (the main alternative anxiolytic/hypnotic drugs) than for quetiapine.

Ultimately, any clinical decision to use quetiapine off-label has to include an assessment of risks and benefits. Based on published data, there is a solid evidence base to support short term or intermittent use of low doses (up to 150 mg/day) in symptomatic anxiety (e.g. in the context of a major depressive illness), in GAD, and for doses of 25–50 mg/day in insomnia.

Short-term use in other anxiety disorders is also supported by published data. This type of off-label use pattern would be consistent with a previous report from a more methodologically rigorous survey.\textsuperscript{3} The use of quetiapine in these circumstances is not risk-free, however the reduced potential for abuse and dependence over benzodiazepines, the main alternative drug class with a rapid onset of action, is an important consideration.

The case for using quetiapine long term or at higher doses in any of the above symptoms/indications is much less clear, with few published data to support such use. Any decision to prescribe in this way would involve a risk/benefit decision for an individual patient, and would at minimum require demonstrated intolerance to or
failure of first line medications, along with trials of psychological and/or behavioural treatments.

Medsafe provides a useful guidance on professional and ethical considerations for doctors planning to use approved drugs for unapproved indications, including advice on when and how to use informed consent. The guidance states, “For an unapproved medicine or unapproved use, the consumer should be advised of the unapproved status. The consumer should also be advised of the degree and standard of the support for the use of the medicine…”. The guidance recommends use of written informed consent if the treatment has minimal supporting evidence, if there is equivocal evidence for safety or efficacy, or if the treatment is experimental.

In conclusion, the Canterbury survey identifies that off-label quetiapine use is common. There is a solid evidence base to support its short term low dose use in anxiety and insomnia. As part of an ethical prescribing process, it is important for doctors to highlight to patients the quality of clinical evidence for the proposed off-label use of quetiapine, bearing in mind the Medsafe guidance.

Competing interests: Professor Glue is currently on the Scientific Advisory Board of Demerx Pharmaceuticals, and has attended a scientific advisory board for Janssen. Dr Gale has been on speakers’ bureaux for Lilly and Janssen, and has had travel costs supported by Lilly.

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References:
