Off-label use of atypical antipsychotic medications in Canterbury, New Zealand

Erik Monasterio, Andrew McKean

Abstract

Aim To estimate the frequency and characteristics of “off-label” use of atypical antipsychotic medications (AAPs) by psychiatrists in Canterbury, New Zealand.

Methods Data on “off-label” prescribing of AAPs including the choice of medication, frequency of prescribing, and the indications for its use was collected using a postal survey of psychiatrists registered with the NZ Medical Council in the Canterbury region.

Results 48 psychiatrists (71%) completed the survey. Forty-six (96%) prescribed AAPs “off-label”. By far the most common agent was quetiapine (94%). Twenty-eight respondents (58%) prescribed “off-label” at least once a week. The most common reasons for the use of these agents was: anxiety (89%), sedation (79%), post-traumatic stress disorder (57%), treatment augmentation of another antipsychotic agent (48%) and behavioural and psychological symptoms of dementia (33%).

Conclusion “Off-label” prescribing, particularly of quetiapine is very common in the Canterbury region, despite little scientific evidence for this kind of use, increasing evidence of abuse and potential for significant side-effects.

The term “off-label” for the use of a medication generally relates to the prescription of a drug without approved official authorisation. Within New Zealand this authorisation is provided by Medsafe (the New Zealand Medicines and Medical Devices Safety Authority). For prescription medications the approval process requires robust scientific evidence of efficacy and safety for specific clinical situations.

Off-label prescribing has been around for decades, is relatively common in most aspects of clinical practice and is considered to be legal.\(^1\)

Although conventional antipsychotic medications, such as thioridazine and chlorpromazine have traditionally been prescribed off-label, before the early 1990’s their use was largely reserved for adults with severe psychotic disorders;\(^2\) unpleasant extrapyramidal side-effects and cardiovascular risks arising from widening QTc interval appear to have largely limited their use outside these disorders.

The introduction of better tolerated, second generation atypical antipsychotics (AAPs) such as risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole from the mid-1990s led to a rapid expansion of antipsychotic medication use for a wide variety of unlicensed conditions and in more diverse clinical populations. This unlicensed use has predominantly not been supported by scientific evidence.\(^3\)

Studies examining the use of AAPs across specialist inpatient and outpatient populations and general practice indicate that between 43% and 70% of atypical antipsychotic use is off-label.\(^4\)-\(^9\)
In an illuminating analysis of reports from the 2001 National Disease and Therapeutic Index (which tracks epidemiological trends and treatment patterns among private physicians in the United States) Radley et al found that 73% of the off-label use of 160 commonly prescribed drugs lacked evidence of clinical efficacy, and only 27% was supported by strong scientific evidence: the greatest disparity between supported and un-supported off-label uses was found among prescriptions for psychiatric uses (4% strong support vs. 96% limited or no support). Although the literature indicates a high prevalence of off-label prescribing, there is little guidance on how to address this issue or limit the practice.

Expanded use of atypical antipsychotic agents has come with a substantial cost burden. In NZ the cost of all antipsychotics was $23.1 million in 2000 and the cost for only AAPs rose to $54.5 million in 2010 (Personal Communication: G MacGibbon, PHARMAC, 27/10/2010). In 2007 US spending on AAPs was estimated at US$13.1 billion, exceeded only by lipid regulators and proton pump inhibitors.

Peer-reviewed scientific publications have paid substantial recent attention to reporting on the illegal promotion of off-label prescribing by pharmaceutical companies and the legal repercussions of this practice; these illegal marketing efforts would appear to have substantially contributed to the expanded use of AAPs.

Within the United States the Food Drug Administration (FDA) has been criticized for its poor monitoring of drug companies promotion of off-label uses of their drugs. Recent landmark legal cases by the US Department of Justice, charging that the drug companies Eli Lilly and AstraZeneca illegally promoted the off-label use of the AAPs olanzapine and quetiapine have settled before trial for payments of US$1.4bn and US$520m respectively.

In commenting on the legal case against AstraZeneca US Attorney General Eric Holder said that illegal acts by drug companies “can put the public health at risk, corrupt medical decisions by health care providers, and take billions of dollars directly out of taxpayers’ pockets.”

Determining the appropriateness of off-label prescribing in current clinical practice is particularly challenging as physicians must weigh up risks and benefits of various medications across diverse clinical presentations, with limited scientific evidence of efficacy, and under pressure from various stakeholders including patients, advocacy groups, medical staff and the pharmaceutical industry.

The frequency and characteristics of off-label AAPs prescribing in New Zealand is not known. It is the author’s clinical experience (in New Zealand) that the off-label use of AAPs is common in primary and specialist care settings. The aims of this study were to ascertain the frequency, patterns and characteristics of off-label prescribing of AAPs.

**Methods**

Psychiatrists in Canterbury, New Zealand were identified through the New Zealand Medical Council website. A postal survey and an addressed return envelope were sent to all psychiatrists based in Canterbury (pop. 504,000), New Zealand between January and February 2010. The questionnaire was anonymous and asked about generic prescribing and the characteristics of off-label prescribing of AAPs: The choice of medication, frequency of prescribing, and the indications (ranked in order of frequency).
Results were collated and analysed on an Excel spreadsheet (Microsoft, USA).

**Results**

There was a 71% (48/68) response rate. Of the 48 who responded to the questionnaire, 37 (77%) always prescribed generically and 11 (23%) sometimes prescribed generically. Forty-six (96%) had prescribed AAPs for an off-label indication.

Of those psychiatrists that had prescribed AAPs for an off-label indication, the most common first-line agent was quetiapine (94%) followed by olanzapine (2%), risperidone (2%) and clozapine (2%).

With respect to the frequency of off-label prescribing: 3 (6%) did so on a daily basis; 13 (27%) two to three times a week; 12 (25%) once a week; 7 (15%) every 2 weeks and 13 (27%) once a month.

The most common indications for off-label use are summarised in Table 1. The majority of psychiatrists prescribed AAPs for anxiety (89%) and sedation (79%), followed by symptoms of post-traumatic stress disorder (57%) and treatment augmentation of another antipsychotic agent (48%).

Other relatively common indications include management of behavioural and psychological symptoms of dementia (33%), adjustment disorder (20%) and psychotic symptoms of Parkinson’s disease (20%).

**Table 1. Indications for off-label AAPs prescribing**

<table>
<thead>
<tr>
<th>Off-label indication</th>
<th>Percentage of psychiatrists that prescribed for this indication</th>
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<tbody>
<tr>
<td>Anxiolytic</td>
<td>89 %</td>
</tr>
<tr>
<td>Sedative</td>
<td>79 %</td>
</tr>
<tr>
<td>PTSD</td>
<td>57 %</td>
</tr>
<tr>
<td>Augmentation of another antipsychotic</td>
<td>48 %</td>
</tr>
<tr>
<td>Behavioral and psychological symptoms of dementia</td>
<td>33 %</td>
</tr>
<tr>
<td>Adjustment disorder</td>
<td>30 %</td>
</tr>
<tr>
<td>Delirium</td>
<td>20 %</td>
</tr>
<tr>
<td>Parkinson's disease - psychotic disorder</td>
<td>20 %</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>11 %</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>9 %</td>
</tr>
<tr>
<td>Gilles de la Tourette's syndrome</td>
<td>9 %</td>
</tr>
<tr>
<td>Behavioral disturbance/impulsivity in children without ADHD</td>
<td>4 %</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 %</td>
</tr>
<tr>
<td>Agitation/ Overarousal</td>
<td>2 %</td>
</tr>
<tr>
<td>Behavioral disturbance in ID</td>
<td>2 %</td>
</tr>
<tr>
<td>Huntington's Disease</td>
<td>2 %</td>
</tr>
<tr>
<td>To target depressive ruminations and aid sleep</td>
<td>2 %</td>
</tr>
</tbody>
</table>

**Discussion**

The findings of the current survey support the observations of a number of other studies which highlight a high frequency of off-label use of AAPs across diverse patient populations.\(^5\)\(^-\)\(^10\)\(^,22\) The results reveal high levels of off-label prescribing...
amongst Christchurch psychiatrists, with most prescribing generically. The reported rate of 96% is significantly higher than the 65% rate of off-label use found in a 2000 British study with similar methodology. Whether this is due to overall higher use in NZ, a local phenomenon or a reflection of increased use over time is not possible to determine from our data.

The systematic literature reviews that have examined off-label use of AAPs indicate that there is no current evidence for monotherapy in the management of anxiety disorders, although there is some evidence to support the use of: adjunctive risperidone in the treatment of refractory obsessive compulsive disorder, post-traumatic stress disorder, pervasive developmental disorder and Tourette’s syndrome; and olanzapine in the treatment of refractory depression and borderline personality disorder. Given that the most common symptoms and conditions for which these agents were used included anxiety, sedation and PTSD, it is important to note a general lack of evidence in support of the current use of off-label AAPs.

However, perhaps the most striking finding of the survey is the extent to which quetiapine is the most commonly prescribed off-label agent: it is the first preferred choice of 94% of respondents, and more than half of all respondents prescribed this medication off-label every week. A recent study examining the use quetiapine in an inpatient setting over an 18 month period determined that it was used for licensed conditions in only 25% of patients. Although the extent to which side-effects are dose related is still debated, short- and long-term use of quetiapine is associated with an increased risk of side-effects including weight gain, dyslipidaemia and insulin resistance.

It is also important to note that cases of quetiapine abuse have been increasingly reported in the literature. In the USA it has been referred to as Quell, Susie-Q, Baby Heroin and Q-Ball: It has reportedly been crushed and administered intranasally and intravenously. The annual cost of quetiapine in NZ to May 2010 was $13.5 million (excluding any confidential rebates) and with an estimate that up to 70% of its use is off-label, the cost burden approximately $9.5 million per year or 17% of the total annual cost for all AAPs. However this cost has decreased with the introduction of cheaper generics in August 2010.

Limitations to this study include the retrospective nature of the survey, and the possibility that psychiatrists do not have an accurate recollection of the information requested. In order to ensure anonymity, information on the specialty area where psychiatrists worked was not requested, therefore it is not possible to determine to what extent off-label use in our survey reflects prescribing practices in areas of particular concern, such as child and adolescent and elderly services.

Conclusion

In summary, off-label use of AAPs, particularly quetiapine appears to be common in current specialist mental health practice, despite limited scientific support for this kind of use. Considering that even low dose AAPs can have significant side-effects, are of unknown efficacy, and appear to have a potential for abuse, we recommend a more considered and measured approach to their use.
There is a pressing need to know to what extent they are used in primary care settings, what factors contribute to their popularity and to ensure that patient safety is not jeopardised and valuable resources are not wasted.

We recommend that whenever these agents are used off-label, informed consent is obtained, treatment is monitored, and an end- or review point of treatment is identified.

Competing interests: Dr E Monasterio has received honoraria presentation payments and travel and accommodation assistance from Janssen-Cilag, Eli Lilly and Sanofi-Aventis. A McKean has received travel assistance and accommodation payments from Janssen-Cilag and Sanofi-Aventis to attend meetings.

Author information: Dr Erik Monasterio, Senior Clinical Lecturer, University of Otago and Consultant in Forensic Psychiatry, Hillmorton Hospital, Christchurch; Andrew McKean, Senior Pharmacist, Hillmorton Hospital, Christchurch

Acknowledgements: The authors thank Dr Matthew Croucher, Dr Ceri Evans and Professor Les Toop for their help with the manuscript.

Correspondence: Dr Erik Monasterio, Medlicott Academic Unit, Hillmorton Hospital, PO Box 4733, Christchurch, New Zealand. Fax: +64 (0)3 3391148; email: erik.monasterio@cdhb.govt.nz

References:


