Quetiapine Nation? 300% increase in quetiapine prescriptions by family physicians in Canada from 2005 to 2012.

Tamara Pringsheim MD MSc[1], and David M. Gardner BSc Pharm, ACPR, PharmD, MSc[2]

[1]Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada

[2]Department of Psychiatry and College of Pharmacy, Dalhousie University, Halifax, NS, Canada

Corresponding Author:

Tamara Pringsheim, MD MSc
Alberta Children's Hospital
2888 Shaganappi Trail NW
Calgary AB T3B 6A8
Phone (403) 955-7921
Fax (403) 955-5990
Email tmprings@ucalgary.ca

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Abstract

Background: Antipsychotic use has experienced an unprecedented rate of growth in the last decade, primarily related to non-psychotic indications and off-label use. The increased use of antipsychotics is concerning due to high rates of metabolic and extrapyramidal side effects, and inadequate monitoring for these complications.

Method: We performed analyses on national antipsychotic use with the IMS Brogan Canadian CompuScript Database and the Canadian Disease and Treatment Index. We analyzed the number of dispensed prescriptions for second generation antipsychotics by family physicians and psychiatrists, and diagnoses associated with recommendations for quetiapine by family physicians and psychiatrists, from 2005 to 2012.

Results: Between 2005 and 2012 there was a 300% increase in dispensed prescriptions for quetiapine by family physicians, from 1.04 million dispensed prescriptions in 2005, to 4.17 million in 2012. In comparison, dispensed prescriptions by family physicians for risperidone and olanzapine increased by only 37%. Dispensed prescriptions for quetiapine by psychiatrists increased 141%, from 0.87 million dispensed prescriptions in 2005, to 2.11 million in 2012. Accounting for 79% of quetiapine recommendations, the top four diagnoses associated with quetiapine in 2012 were mood disorders, psychotic disorders, anxiety disorders, and sleep disturbances. A ten-fold increase in quetiapine recommendations for sleep disturbances was seen over the eight year study period, with almost all recommendations coming from family physicians.

Conclusion: These findings indicate a large and preferential increase in the use of quetiapine over other antipsychotics in Canada, and that expanded use is mostly due to an increase in its off-label prescribing by family physicians.

Background

Antipsychotic use has experienced an unprecedented rate of growth in the last decade, primarily related to new, non-psychotic indications and off-label use across all age groups in Canada(1-3). Second-generation antipsychotics (SGAs) are preferred by prescribers primarily because of their lower risk for movement disorders(4). However, usage patterns vary considerably among the SGAs in clinical practice, especially when contrasting olanzapine, which is most commonly used for chronic psychotic disorders, risperidone, with its mixed use in psychosis and in young people with disruptive disorders, and quetiapine, which has become commonplace treatment for mood, anxiety, and sleep problems(1, 5-7). The evidence-base for these expanded uses is often insubstantial or, in the case of quetiapine as a hypnotic, completely inadequate.

Originally indicated for schizophrenia, quetiapine now has Health Canada and US Food and Drug Administration (FDA) indications for the management of bipolar mania and depression as well as for major depressive disorder (MDD)(8, 9). For MDD, it is to be reserved for treatment failures to standard therapies(10) or used as a treatment adjunct(11). It is not indicated for anxiety or sleep disturbances. Regarding its application for approval to treat generalized anxiety disorder, the FDA stated concerns about its long-term metabolic and movement disorders risks and its association with sudden cardiac death(12). The manufacturer retracted its application for an anxiety disorder indication globally several years ago.

Quetiapine and its active metabolite norquetiapine are both potent antihistamines(13). This, possibly among other pharmacological actions, accounts for quetiapine's hypnotic effect and increasing popularity as a sleeping aid when used at lower doses(14, 15). At intermediate doses, putative antidepressant and

anxiolytic pharmacological actions become relevant. Norquetiapine and, to a lesser extent, quetiapine are 5-HT_{1A} agonists and norquetiapine is a moderately potent re-uptake inhibitor of noradrenaline. However, quetiapine and its several metabolites are pharmacologically diverse and carry risks that make quetiapine a poor choice, based on tolerability and safety concerns and regardless of its efficacy, in the routine management of insomnia, anxiety, and depression(4, 12).

We measured the rise in use of quetiapine and other SGAs among family physicians and psychiatrists and specifically investigated the most common diagnoses associated with quetiapine recommendations, including its rate of use for the treatment of mood, psychotic, and anxiety disorders as well as sleep disturbances.

Methods

IMS Brogan (IMS) is a proprietary source of pharmacoepidemiologic data. The IMS databases are the only national source for population based data on antipsychotic medications in Canada. Administrative data cannot be used for this purpose because, in most Canadian provinces, administrative records for prescription data are only collected in special population groups, e.g. those covered by publicly funded drug plans, and the extent of coverage differs across provinces. Several national surveys have collected information on medication use (e.g. the National Population Health Survey), but no surveys having an adequate sample size have targeted this specific group.

We performed analyses based on the IMS Brogan Canadian CompuScript Database and the Canadian Disease and Treatment Index (CDTI). The Canadian CompuScript database contains national prescription data collected in pharmacies at the time prescriptions are filled, and records the specialty of the prescribing physician. The data collected from Quebec, Ontario, Alberta, Saskatchewan, Nova Scotia, New

Brunswick, PEI and Newfoundland is tagged with a doctor number or name which allows IMS Brogan to identify the specialty of the prescriber. In British Columbia and Manitoba national estimates are used as a proxy at the provincial level. National estimates of prescribing by specialty are derived through statistical methods that maintain the proportion of physicians in each specialty. Approximately 80% of dispensed prescriptions are reported to IMS. For this study, we analyzed the number of dispensed prescriptions for quetiapine by family physicians/general practitioners and psychiatrists, as well the number of dispensed prescriptions for risperidone, olanzapine, aripiprazole, ziprasidone, clozapine, and paliperidone for comparison purposes. CDTI is a longitudinal national physician panel study. CDTI collects treatment data from a sample of Canadian office-based physicians (n=652) that comprise a representative sample, of which 85% to 91% are respondents from the previous quarter. This study identifies usage and treatment patterns by drug and by physician specialty. Each physician participating in the panel completes a record of all patient visits during a two-day period per quarter. The nature of each visit, including the age and gender of the patient, drug recommendation, and the therapeutic indication are recorded. Physicians are compensated for participation and accuracy. Analyses of the CDTI database allowed us to characterize the frequency with which physicians recommend antipsychotic medications for adults for specific diagnoses. For this study, we used the CDTI database to evaluate diagnoses associated with recommendations for quetiapine by family physicians/general practitioners and psychiatrists.

Results

Quetiapine, risperidone and olanzapine are the three most common antipsychotic medications prescribed by family physicians/general practitioners and psychiatrists. Between 2005 and 2012 there was a 300% increase in dispensed prescriptions for quetiapine prescribed by family physicians/general practitioners, from 1.04 million dispensed prescriptions in 2005, to 4.17 million in 2012. In comparison, dispensed prescriptions prescribed by family physicians/general practitioners for risperidone and olanzapine increased by only 37% over the same time interval. Dispensed prescriptions for quetiapine

from family physicians/general practitioners surpassed prescriptions for the other two medications, with 1.91 million dispensed prescriptions for risperidone and 1.33 million prescriptions for olanzapine in 2012 (see Figure 1).

The total number and rate of increase in dispensed prescriptions for quetiapine was much higher for family physicians/general practitioners compared to psychiatrists. Dispensed prescriptions for quetiapine by psychiatrists increased 141%, from 0.87 million dispensed prescriptions in 2005, to 2.11 million dispensed prescriptions in 2012. Dispensed prescriptions for risperidone increased by 43%, and for olanzapine increased 32% over the same time interval (see Figure 2). In 2005, psychiatrists were prescribing quetiapine, risperidone, and olanzapine at nearly identical rates. By 2012, the use of quetiapine had approximately doubled the rate of the other two antipsychotics.

As estimated from the CDTI, quetiapine recommendations from GPs and psychiatrists increased from 1.15 million in 2005 to 1.92 million in 2012. Accounting for 79% of quetiapine recommendations, the top four diagnoses associated with quetiapine use in 2012 were (1) mood disorders, (2) psychotic disorders, (3) anxiety disorders, and (4) sleep disturbances (see Figures 3-6). Quetiapine recommendations for mood disorders nearly doubled, mostly due to an increase in general practitioner prescribing (Figure 3). For psychosis usage dropped overall, due to fewer recommendations by psychiatrists (Figure 4). Recommendations more than doubled for quetiapine in the treatment of anxiety disorders, spurred on primarily by general practitioner prescribing (Figure 5). A ten-fold increase in quetiapine recommendations for sleep disturbances was seen over the seven year study period, with almost all recommendations coming from general practitioners (Figure 6). The number of recommendations grew disproportionately for women for this indication. In 2005, 51% of the 10,530 recommendations were for women, whereas in 2012 78% of the 101,580 were for women. The greatest surge in the number of recommendations of quetiapine for sleep disturbances was between 2011 (66.7% in women) and 2012,

in which an additional 32,350 recommendations were observed representing a 47% increase year over year.

Interpretation

These findings indicate a large and preferential increase in the use of quetiapine over other antipsychotics in Canada. They show that quetiapine's expanded use is mostly due to an increase in its off-label prescribing by GPs. Our CompuScript analysis demonstrates that over 50% of filled antipsychotic prescriptions in Canada were for quetiapine in 2012 and that the majority came from primary care physicians. In 2005, the ratio of prescriptions for quetiapine between family physicians and psychiatrists approached 1:1. By 2012, it was 2:1.

Our analyses of the CDTI data demonstrate how the use of quetiapine has changed over time. The data suggest that in 2008 the majority of recommendations for quetiapine were for off-label indications. While there has been a gradual decline in its recommendations for psychosis, other uses have increased steadily. This trend has been observed by others(16, 17). The 2012 findings indicate that for every 100 recommendations for quetiapine, 43 were for mood disorders, 18 for psychosis, 12 for anxiety disorders, 5 for sleep disturbances, and 22 for other indications. In contrast, recommendations were nearly evenly split between psychosis and mood disorders in 2005 with fewer than 1 in 1000 recommendations for sleep disturbance.

Quetiapine's rise in off label use preceded its regulatory approval for depression. The FDA granted approval for quetiapine in the treatment of depression in patients with bipolar disorder in 2006(11). Health Canada approved quetiapine for bipolar mania and depression in 2008(10). Indications for major depression were approved by the FDA (as adjunct treatment) and Health Canada (to treat failures to

standard therapies) in 2009(10, 11). It is possible that the publication of clinical trials evaluating quetiapine for the treatment of depression, or knowledge that it was being investigated for this indication, bolstered its use in the treatment of mood disorders. In their systematic review, Komossa and colleagues identified 7 blinded, randomized trials published in peer-reviewed journals between 2006 and 2009(18). The findings of this review suggest that quetiapine be reserved for second or third-line therapy in depression. Numbers needed to treat (NNT) for response, remission, and discontinuation due to adverse effects approximate 8, 17, and 11, respectively, versus placebo. When used as an add-on to unsuccessful antidepressant therapy, the NNTs are estimated to be 10, 8, and 12, respectively. The only direct comparison with an antidepressant involved duloxetine, which may be less effective and less tolerable than other antidepressants(19), found no between group differences in efficacy but reduced overall tolerability with quetiapine (i.e., NNT for discontinuation due to adverse effects of 6)(20).

Quetiapine's use in anxiety is remarkable and unprecedented for an antipsychotic. While several small randomized trials were completed and published earlier, the first large RCT of quetiapine for anxiety was published in a peer-reviewed journal in 2010 followed by four others in the following 2 years. Earlier versions of theses studies were presented at international meetings and were included in a systematic review(21). While the findings indicate clinical efficacy in generalized anxiety, quetiapine's overall tolerability was poor. Odds for adverse effect related dropouts were 3.8 and 2.2 times higher with quetiapine compared to placebo and antidepressant comparators (i.e., paroxetine, escitalopram), respectively(21-23).

Patten and colleagues reported an estimated 108,000 recommendations for tricyclic antidepressants (TCAs), primarily amitriptyline, and 168,000 recommendations for trazodone for sleep disturbance in 2005(24). In 2012, quetiapine reached approximately the same level of use as the TCAs and, based on trends observed in the CDTI data, it has now likely exceeded that of the tricyclics and is approaching the

rate of use of trazodone for sleep disturbances. The evidence supporting quetiapine as a hypnotic agent is limited(7). Two randomized polysomnographic studies have been conducted, involving a total of 34 participants, 16 with primary insomnia and 18 as healthy volunteers(25, 26). In the study of 16 subjects with primary insomnia, baseline characteristics were not balanced with the quetiapine group having notably worse sleep measures(25). The study showed no difference between treatment groups after 14 days, possibly as a result of these differences at baseline. In a study of 18 volunteers, all participants were exposed to placebo, quetiapine 25 mg, and quetiapine 100 mg on two consecutive nights with 4 day intervening washouts(26). Both doses showed advantage in terms of total sleep time (added 30 to 45 minutes) and reduced sleep onset latency under noisy conditions (by 15 to 20 minutes). However, time to achieve slow wave sleep was delayed with quetiapine 25 mg and 100 mg (by 13 and 30 minutes on average, respectively) and quetiapine was associated with more periodic limb movements (PLMs): placebo 34 PLMs, quetiapine 25 mg: 57 PLMs, and quetiapine 100 mg: 155 PLMs). In addition, two participants were removed due to fainting with quetiapine 100 mg.

It is not known, from controlled trials, if quetiapine's sedative effects are sustained over time or if low-dose use provides a favourable risk-benefit ratio compared to alternative sleep aids in patients with non-affective insomnia. An open-label, uncontrolled study of 18 primary insomnia patients with a baseline total sleep time of 6 hours showed an increase of 48 minutes after two weeks and 38 minutes at 6 weeks. Just over half took 25 mg per night and the rest 50 or 75 mg. Sleep onset and slow wave sleep time were not significantly improved(14). The relative effectiveness, tolerability, and safety of quetiapine when compared to other commonly used hypnotics is a matter of speculation as there are no direct comparisons.

Quetiapine and its active metabolite norquetiapine are potent antihistamines, which likely accounts for much of quetiapine's sedating effect. However, unlike diphenhydramine, the prototypical centrally acting

antihistamine, quetiapine and norquetiapine have several, clinically relevant, other pharmacological actions worth considering. Most importantly, quetiapine is a D_2 antagonist. It has low potency at this receptor necessitating higher doses to achieve antipsychotic effects. However, like all antipsychotics, it is a common cause of akathisia and a rare cause of neuroleptic malignant syndrome(4, 27). The risk for developing a severe movement disorder when used at lower doses (e.g., 25 to 150 mg/day) in the treatment of anxiety and sleep disturbance has not been sufficiently investigated. It is well recognized for its ability to exacerbate cardiovascular risk factors including hypertension, dyslipidemia, and obesity, including when used at lower doses for insomnia(4, 9, 28). Less well recognized are risks of severe hepatitis, potentially chronic movement disorders, pneumonia, hypothyroidism, and confusion(4, 9, 29-32). Quetiapine is anticholinergic, as indicated by norquetiapine's affinity for M1 receptors, and can produce blurred vision among other anticholinergic side effects(9, 13). Relevant to its use in anxiety and insomnia, quetiapine has been repeatedly associated with withdrawal reactions as well as abuse and dependence(33, 34).

In addition to concerns of over use of quetiapine in treating patients with major depression, anxiety, or sleep problems, we have concerns about inadequate monitoring of patients of all ages taking quetiapine and other antipsychotics(4, 35). This issue is most pressing for quetiapine considering its widespread off label use(36). We recommend that clinicians adhere to published monitoring guidelines when using quetiapine, whether for approved indications or off-label, regardless of the dose used. Depending on the patient, these can include vitals, weight, BMI, waist circumference, lipids, fasting glucose and insulin, and TSH. Moreover, patients should be informed of their treatment options, pharmacological and non-pharmacological, along with a review of the related potential harms and benefits.

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Figure 1

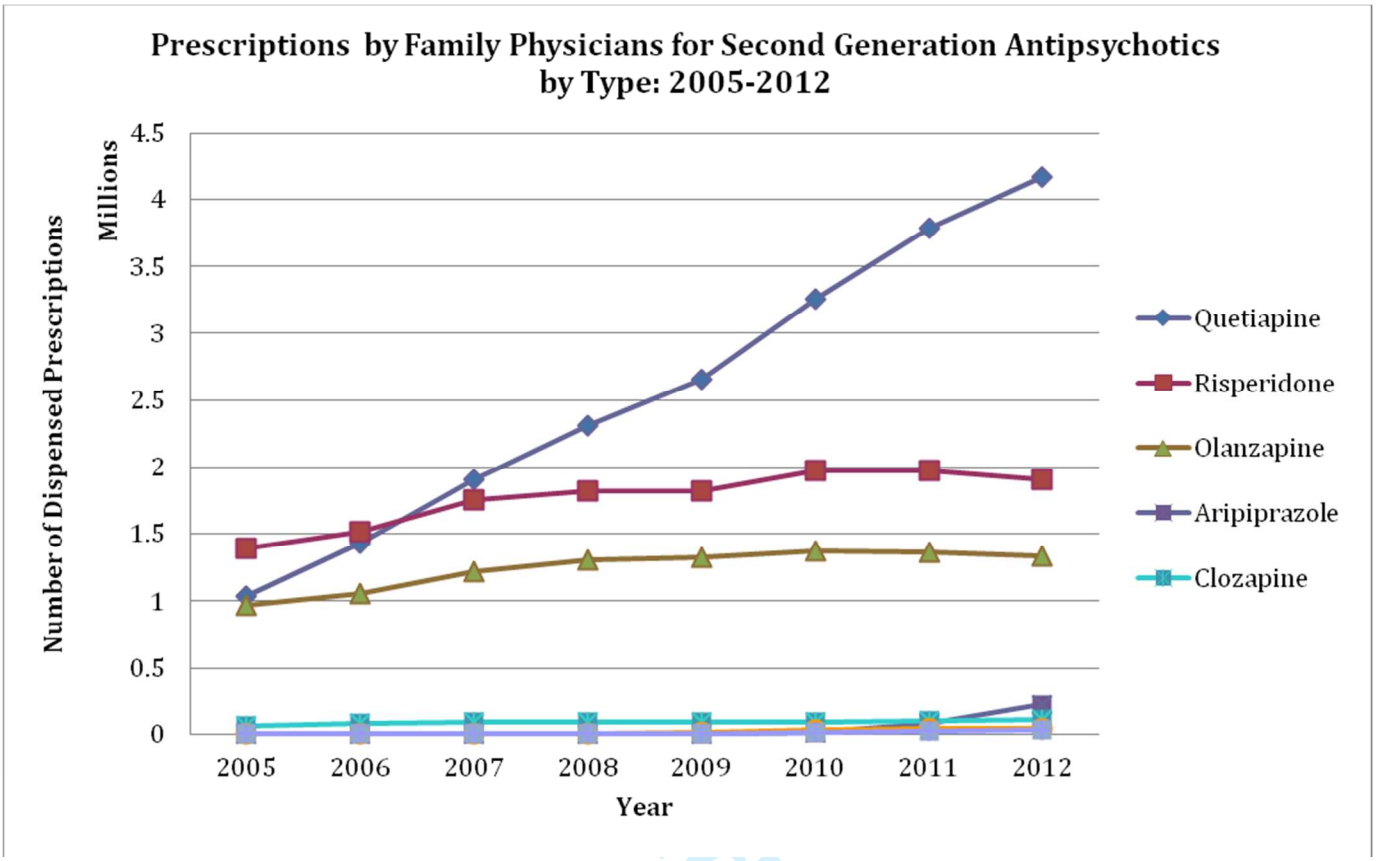

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Figure 2

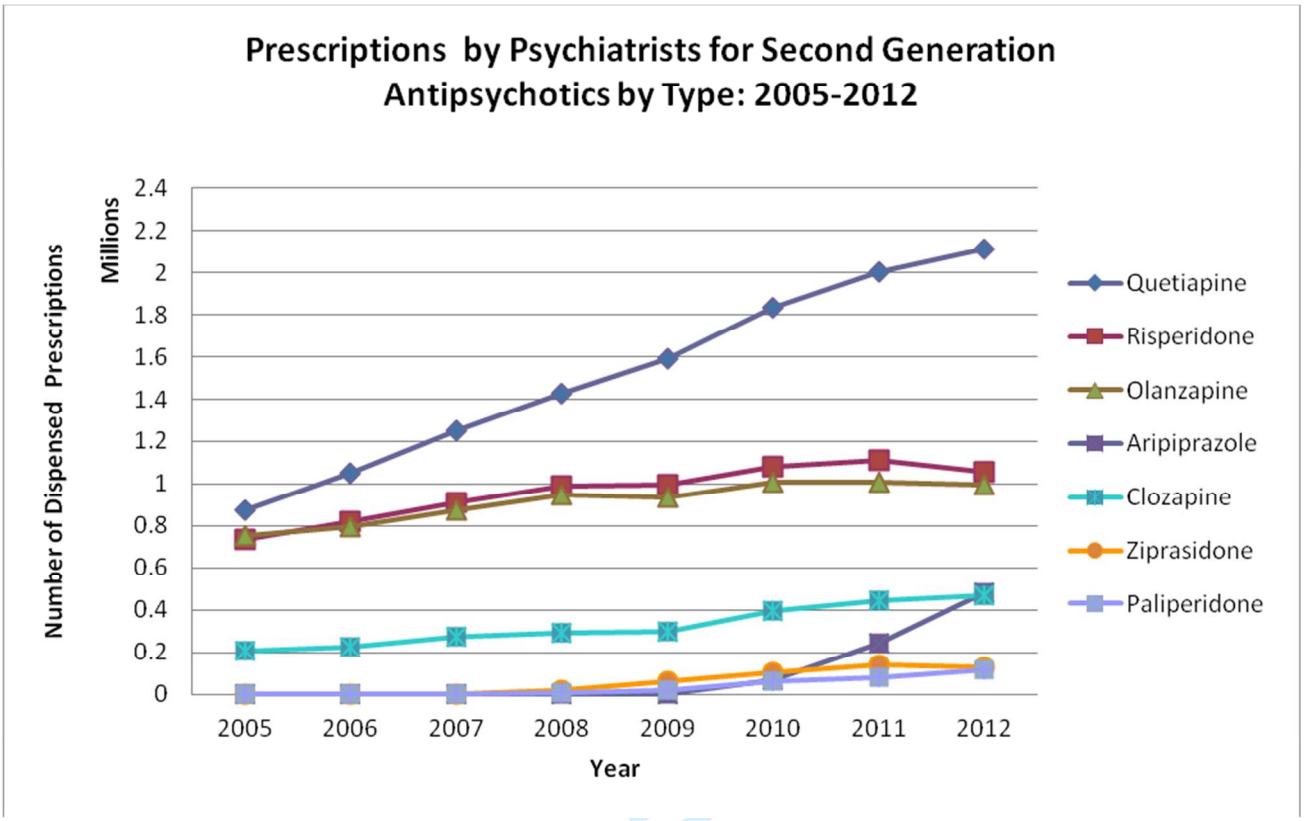

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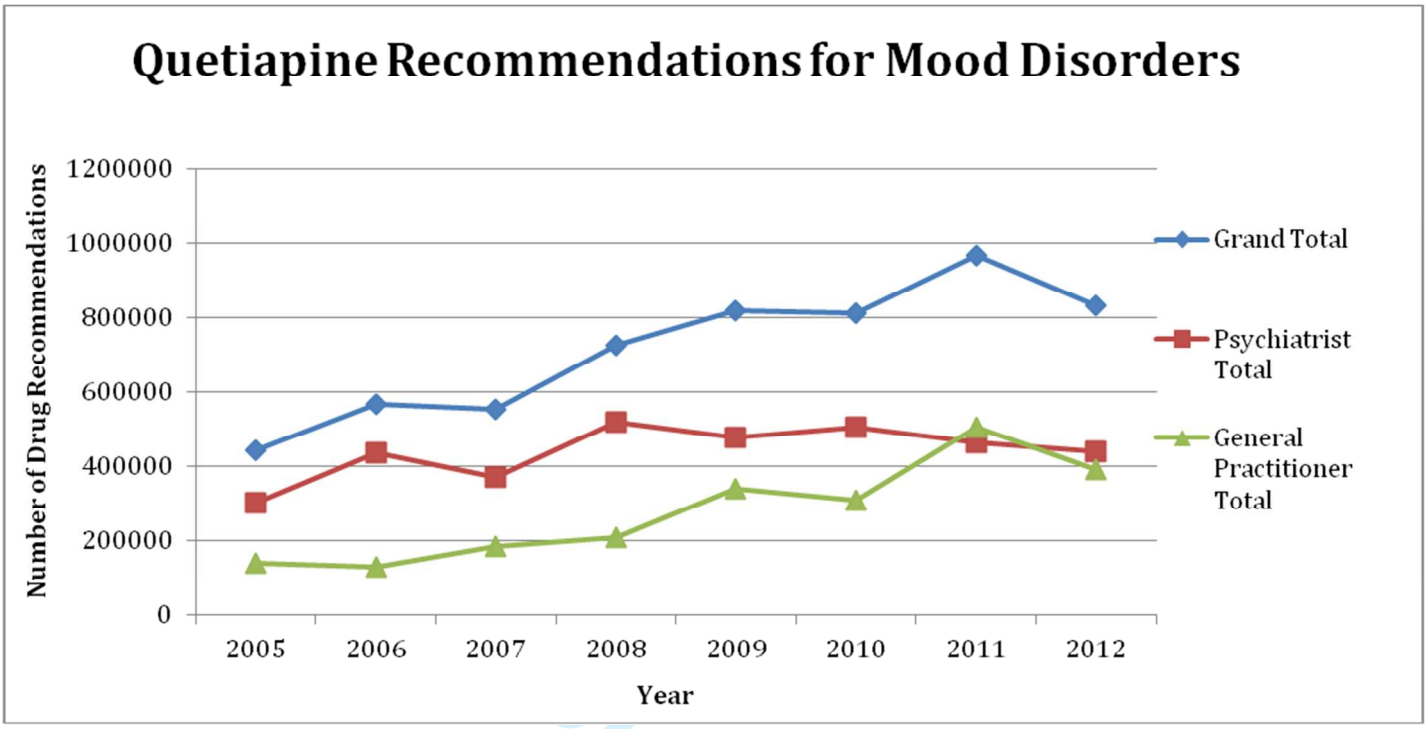
Figure 3



Source: IMS Brogan Canadian Disease and Therapeutic Index

Figure 4

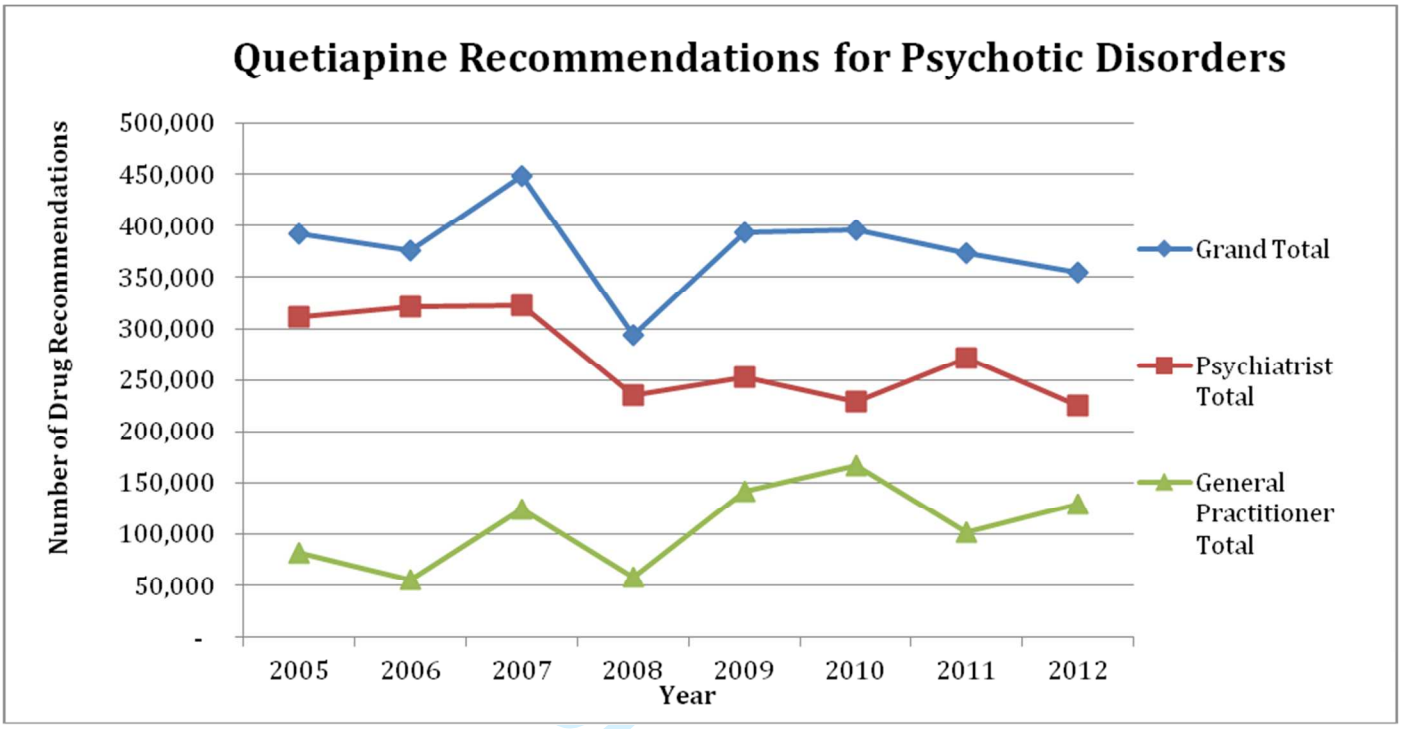


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Figure 5

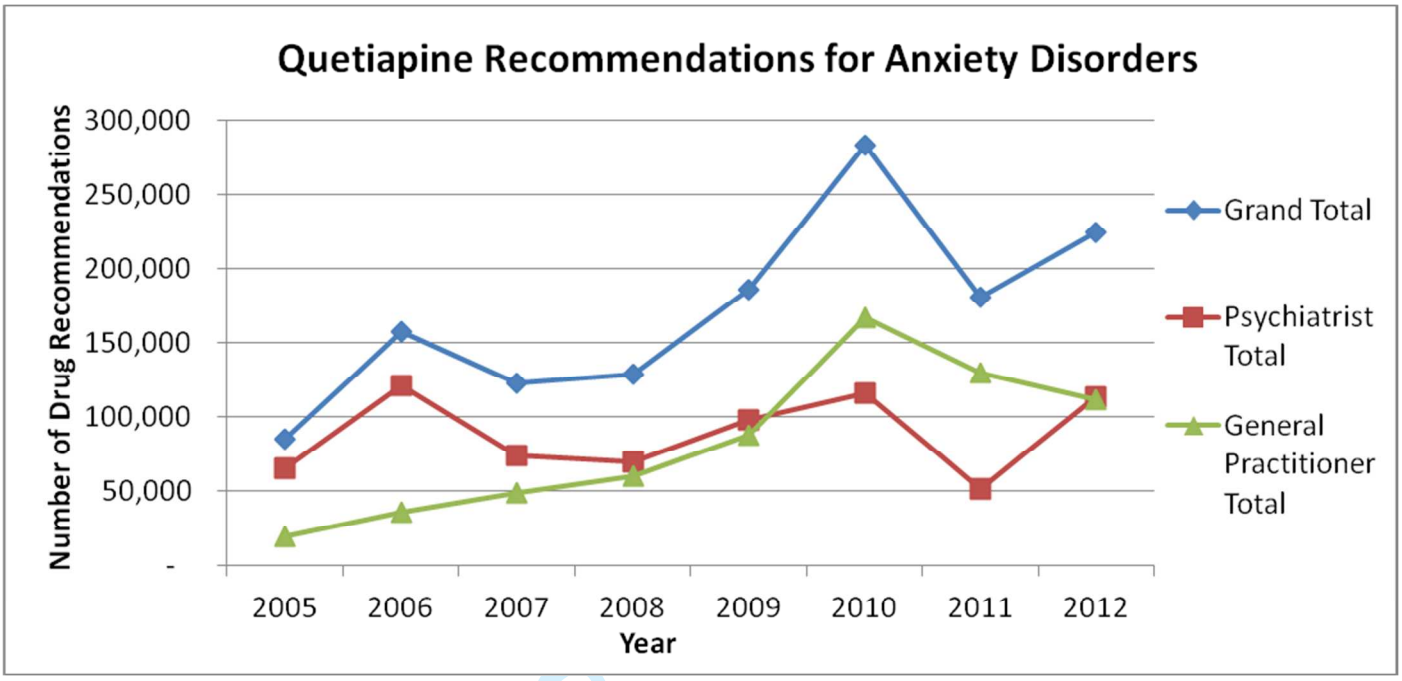

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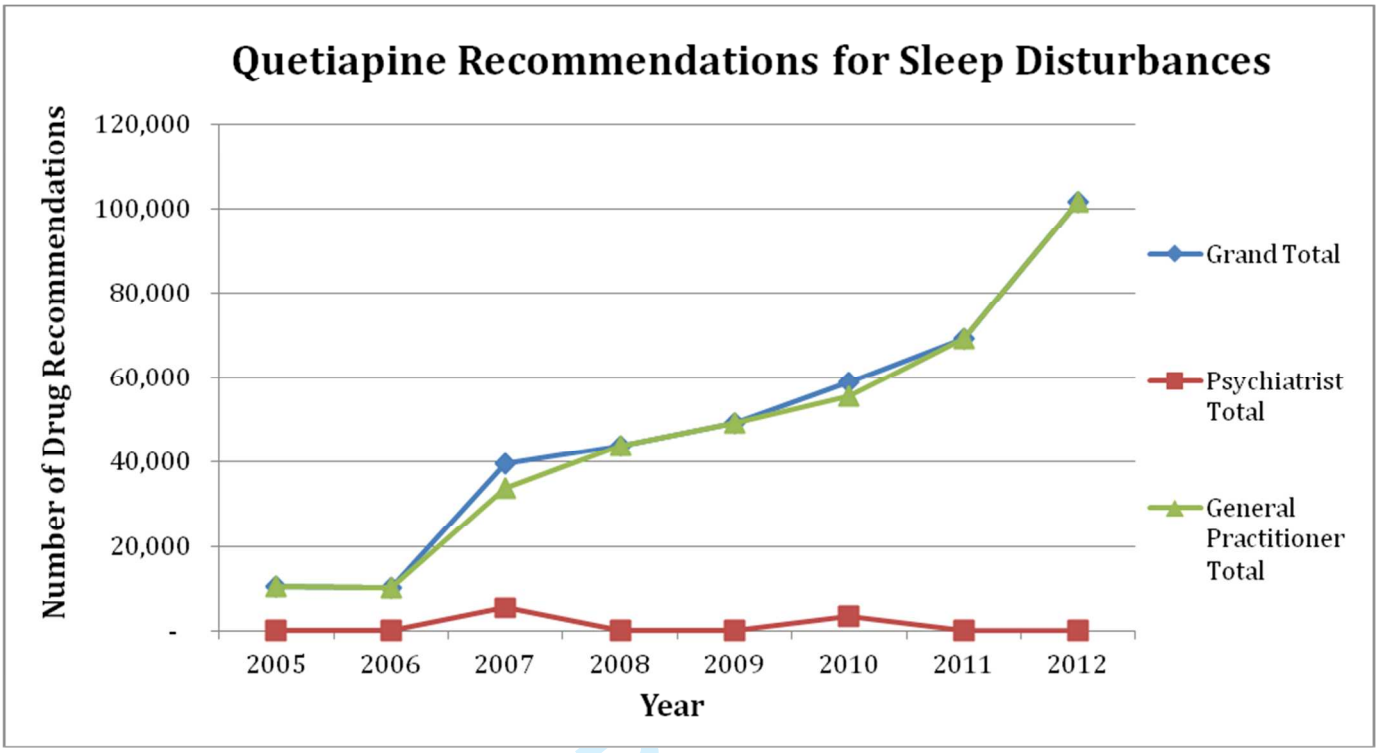
Figure 6



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