

PSYCHOPHARMACOLOGY

Prescribing Practices of Quetiapine for Insomnia at a Tertiary Care Inpatient Child and Adolescent Psychiatry Unit: A Continuous Quality Improvement Project

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Abstract

Objective: To examine the prescribing practices of quetiapine for insomnia at a tertiary care child and adolescent psychiatric inpatient unit. **Method:** A retrospective chart review was conducted on all admissions in 2013 involving night-time only prescription of quetiapine. We examined patient demographics, discharge diagnoses, physician's written indications for prescriptions, and maximum doses used. If used for insomnia only, we noted any documentation of past sedative trials, concurrent prescriptions of other sedative agents, whether quetiapine was started in hospital or continued as a part of a community regimen, and whether quetiapine was continued on discharge. **Results:** Of 720 admissions, 83 (11.5%) involved the prescription of night-time only quetiapine, and 47 of the 83 (57%) were for insomnia only. Of patients prescribed quetiapine for insomnia only, most common discharge diagnoses were anxiety disorder (35%), depressive disorder (27%), eating disorder (27%), and Cluster B/borderline personality traits/disorder (25%). Mean age was 15.4 years; mean maximum dose was 41.2mg. Quetiapine was often started during admission (89.5%) and continued on discharge (66%). About 40% of these cases involved concurrent prescription of other sedative agents. Most patients (81%) had no documented history of prior sedative trials. **Conclusions:** Quetiapine is used not infrequently for the management of insomnia in adolescents in tertiary mental health settings. We highlight the nuances associated with the prescription of quetiapine for the treatment of insomnia in the unique setting of the child and adolescent psychiatric inpatient unit, emphasizing the importance of weighing short-term use with potential long-term adverse consequences if continued in the community setting.

Key Words: *quetiapine, insomnia, antipsychotics, inpatient, off-label*

Résumé

Objectif: Examiner les pratiques de prescription de quétiapine pour l'insomnie dans une unité psychiatrique de soins tertiaires pour enfants et adolescents hospitalisés. **Méthode:** Un examen des dossiers rétrospectif a été mené pour toutes les admissions de 2013 impliquant une prescription de quétiapine pour la nuit. Nous avons examiné les données démographiques des patients, les diagnostics au congé de l'hôpital, les indications de prescriptions écrites par le médecin, et les doses maximum utilisées. Si la quétiapine était utilisée pour l'insomnie seulement, nous avons pris en note toute documentation d'essais passés de sédatifs, les prescriptions concurrentes d'autres agents sédatifs, que la quétiapine ait été commencée à l'hôpital ou qu'elle soit poursuivie dans le cadre d'une pharmacothérapie communautaire, ou encore

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qu'elle soit continuée au congé. **Résultats:** Sur 720 admissions, 83 (11,5 %) impliquaient la prescription de quétiapine de nuit, et sur ces 83, 47 (57 %) étaient pour insomnie seulement. Sur les patients à qui la quétiapine a été prescrite pour insomnie seulement, les diagnostics au congé les plus communs étaient un trouble anxieux (35 %), un trouble dépressif (27 %), un trouble alimentaire (27 %), et un trouble/traits de personnalité limite du groupe B (25 %). L'âge moyen était 15,4 ans, et la dose maximum moyenne était 41,2 mg. La quétiapine était souvent commencée durant l'hospitalisation (89,5 %) et poursuivie au congé (66 %). Quelque 40 % de ces cas impliquaient une prescription concurrente d'autres agents sédatifs. La plupart des patients (81 %) n'avaient pas d'antécédents documentés d'essais de sédatifs antérieurs. **Conclusions:** La quétiapine n'est pas rarement utilisée pour la prise en charge de l'insomnie chez des adolescents dans des établissements de soins de santé mentale tertiaires. Nous présentons les nuances associées à la prescription de quétiapine pour le traitement de l'insomnie dans le contexte unique d'une unité psychiatrique pour enfants et adolescents hospitalisés, en soulignant l'importance d'évaluer l'utilisation à court terme contre les conséquences indésirables potentielles à long terme si l'utilisation se poursuit en milieu communautaire.

Mots clés: quétiapine, insomnie, antipsychotiques, patient hospitalisé, usage non indiqué

Introduction

The emergence and increasing use of atypical antipsychotic agents has occurred in the past two decades. Prescription of such agents has not only been for indicated reasons, but also non-indicated or “off-label” reasons as well (Carton et al., 2015). Studies on prescribing patterns have noted marked increases in atypical antipsychotic prescriptions across the lifespan (Alexander, Gallagher, Mascola, Moloney, & Stafford, 2011; Briesacher et al., 2005; Alessi-severini, Biscontri, Collins, Sareen, & Enns, 2012). Increases in antipsychotic use have been particularly pronounced in children and adolescents (Olfson, Blanco, Liu, Wang, & Correll, 2012; Pringsheim, Lam, & Patten, 2011), and this patient population is the focus of this paper.

Only a small proportion of these prescriptions are for young patients with psychotic disorders, with much higher use in those with disruptive behaviour, attentive, anxiety, mood, and autism spectrum disorders (Penfold et al., 2013). The use of atypical antipsychotics in children and adolescents requires a careful weighing of risks and benefits, with a major risk being the metabolic effects of such medications. These effects are now well-documented, and necessitate regular metabolic monitoring (Correll, Manu, Olshanskiy, Napolitano, Kane, & Malhotra, 2009; Pringsheim, Panagiotopoulos, Davidson, Ho, & Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children guideline group, 2011).

Atypical antipsychotics are increasingly used by physicians for the off-label reason of insomnia (Hermes, Sernyak, & Rosenheck, 2013; Owens, Rosen, Mindell, & Kirchner, 2010). Quetiapine is an antipsychotic agent commonly used for insomnia, though there remains a lack of robust evidence supporting this use (Panagiotopoulos, Ronsley, Elbe, & Smith, 2010; Anderson & Vande Griend, 2014; Maher et al., 2011). A recent review indicated there have been some studies indicating potential efficacy of such use in the presence of comorbid psychiatric illnesses, such as unipolar and bipolar depression, though again these studies are few in number and do not strongly support the use of quetiapine as a sedative agent given potential safety risks.

As part of the “Choosing Wisely Canada” campaign (<http://www.choosingwiselycanada.org>), a national initiative of which the Canadian Academy of Child and Adolescent Psychiatry is a part, clinicians are specifically advised against prescribing atypical antipsychotics as first line agents for insomnia in children and adolescents. Behavioural modification, sleep hygiene, followed by short-term melatonin use are promoted instead. In the same campaign, clinicians are also advised against routinely prescribing antipsychotics for insomnia in any age group, citing their significant weight gain and metabolic effects as deterrents.

While off-label prescribing practices of quetiapine in an adult inpatient psychiatric facility has previously been studied (Philip, Mello, Carpenter, Tyrka, & Price, 2008), we are unaware of any equivalent study involving child and adolescent inpatients. The purpose of our study was to examine the prescribing practices associated with quetiapine for the off-label reason of insomnia at a large child and adolescent psychiatric inpatient unit over one calendar year (2013).

Due to their sedating properties at low doses, we similarly examined olanzapine and chlorpromazine in this manner, but postulated from clinical experience that use of these agents for insomnia would be minimal compared to quetiapine. We hoped that by better delineating how, when, and to whom quetiapine is prescribed in this off-label manner, we could gain a better sense of the practices of clinicians. In particular, we were curious whether practices in the inpatient setting were reflective of current cautions against the agent's use, and if not, allow for further understanding of why this may be the case.

Methods

The sample for the study included all admissions to the McMaster Children's Hospital's child and adolescent psychiatry unit, located in Hamilton, Ontario, from January 1, 2013 to December 31, 2013. The unit is a 22-bed tertiary care unit for children and youth up to their 18th birthday, serving predominantly Ontario Local Health Integration Network (LHIN) four (Hamilton, Burlington, Brantford, Niagara and Haldimand Norfolk), but accepting patients from out of

Table 1. Cases of night-time (qhs) prescription of antipsychotic agents and their documented reasons

	Insomnia only	Insomnia and other reason	Psychosis	Other	Unknown
Quetiapine	47 (56.6%)*	21 (25.3%)	2 (2.4%)	5 (6.0%)	8 (9.4%)
Olanzapine	0 (0%)	2 (8.3%)	8 (33.3%)	4 (16.7%)	10 (41.7%)
Chlorpromazine	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Percentages are percentages within antipsychotic agent

Table 2. Discharge diagnoses of patients prescribed quetiapine for insomnia only

Anxiety disorder	35.4%
Eating disorder	27.1%
Depressive disorder	27.0%
Borderline/cluster B traits/personality disorder	25.0%
Mood disorder NOS	18.8%
Substance use disorder	18.8%
Psychotic disorder	16.7%
Attention deficit hyperactivity disorder	12.5%
Post-traumatic stress disorder	10.4%
Bipolar affective disorder	10.0%
Disruptive behaviour disorders	6.3%
Adjustment disorder	4.2%

region as needed and as able. The hospital pharmacy database was used to identify all admissions where prescription of night-time only (qhs) quetiapine occurred. Retrospective chart reviews of these cases were conducted using the electronic medical system Sovera. Information about maximum dose used, dosing schedule (as needed [prn] or qhs), and whether the agent was started during admission or was a continuation of a community regimen were recorded. Discharge diagnoses were obtained from the hospital discharge forms completed by physicians for each admission. We sought information about the physician's reason for prescribing quetiapine. We also recorded documentation of past sedative trials, concurrent sedative agents (melatonin, zopiclone, trazodone, ativan; prn or regular), and whether the antipsychotic was continued upon discharge. The same process was completed for antipsychotics olanzapine and chlorpromazine.

Descriptive data analysis was done using SPSS (Version 22).

Results

There were a total of 720 admissions in 2013. Of these admissions, 83 (11.5%) involved the prescription of night-time only quetiapine. Forty-seven of the 83 prescriptions (56.6%) were noted in the chart to be for insomnia only. In comparison, two of the 83 (2.4%) were noted to

be specifically for treatment of psychosis only. Twenty-one of the 83 (25.3%) were prescribed quetiapine for insomnia along with other reasons noted in the chart (e.g. bipolar spectrum disorder, concurrent psychotic disorder, depressive symptoms, post-traumatic symptoms, disruptive behaviour disorders) (Table 1).

In instances where patients were prescribed quetiapine solely for insomnia, the majority were female (71 of 83; 85.5%) and the mean age was 15.4 years (+/-1.2 years 95% CI; min=11 and max= 17). The most common discharge diagnoses of these patients were anxiety disorder (35.4%), depressive disorder (27.1%), eating disorder (27.0%), and Cluster B/borderline personality traits/disorder (25.0%) (see Table 2; note many cases involved patients with multiple discharge diagnoses). Fifty-nine of the 83 admissions (71%) involved two or more diagnoses recorded. Average length of admission was 18.6 days (+/-4.9days 95% CI; min=3 and max=95). Most (61 of 83, or 73.8%) of these patients were prescribed quetiapine for insomnia on a routine as opposed to an as needed basis. Mean maximum prescribed dose of quetiapine was 41.2 mg (+/- 24.5mg 95% CI; min=12.5 & max=100mg). In a vast majority (74 of 83 admissions, or 89.5%), patients had not been on quetiapine prior to admission. In 55 of the 83 cases (66%), quetiapine was continued on discharge. Thirty-three of the 83 cases (40%) had other sedative agents prescribed on an as needed basis at bedtime along with quetiapine (melatonin 23%, zopiclone 8%, trazodone 7%, ativan 2%) and 67 of the 83 cases (81%) had no documented history of prior trials of sedatives prior to admission.

We found no cases of olanzapine being used solely for insomnia. There were two cases in which olanzapine was prescribed for insomnia along with another reason. Olanzapine was discontinued prior to discharge for both of these youth. One youth was prescribed chlorpromazine for insomnia only. (See Table 1.)

Discussion

Based on our chart review of the inpatient unit in 2013, quetiapine was prescribed solely for insomnia in 56.6% (47 of 83) of all night-time only quetiapine prescriptions, and for insomnia jointly with another reason in 25.3% (21 of 83). This corresponds to 6.5% (47 of 720) and 2.9% (21 of 720) of all youth admitted to the inpatient unit that year respectively. There is a lack of available studies examining

quetiapine use for insomnia in the inpatient child and adolescent population for comparison. However, these percentages seem quite high given the lack of evidence supporting use of quetiapine for insomnia. There are significant metabolic effects such as weight gain, dyslipidemia, and insulin resistance associated with quetiapine, and the benefits of quetiapine use must be carefully weighed with these adverse effects.

There may be several reasons for this level of use of quetiapine for insomnia in our examined population. Given the tertiary care setting, youth may be presenting with potentially more severe, chronic, or treatment refractory type presentations than would be seen in other settings. We found that youth prescribed quetiapine solely for insomnia had a longer average length of stay (18.6 days) when compared to the typical expected length of stay on our unit (nine days, as tracked by our unit statisticians), suggesting perhaps more complex treatment issues in this population. As well, the majority of youth prescribed quetiapine for sleep appear to be females, with the diagnoses of anxiety disorder, eating disorder, borderline personality disorder or cluster B traits, and depressive disorders being most common. Unfortunately, we do not have diagnostic or demographic data available for our 2013 admissions for comparison, and thus we cannot draw conclusions about whether certain diagnostic entities were over-represented in our group of youth prescribed quetiapine for insomnia. We do note that the percentage of those with borderline personality disorder/cluster B traits in our sample is not considered high compared to other studies which have measured the rate of borderline personality disorder in adolescent inpatient units to be 33-53% (Glenn & Klonsky, 2013; Becker, Grilo, Edell, & McGlashan, 2002; Levy et al, 1999). It is not known if there is particular utility of quetiapine in youth with this cluster of symptoms. While there is a paucity of data addressing the utility of quetiapine in borderline personality disorder (Masi, Milone, Veltri, Iuliano, Pfanner, & Pisano, 2015), one very small available open-label, pilot study has indicated possible reduction of depressive symptoms, anxiety, irritability, intentional self-injury, suicidal tendencies, and affective instability in children and adolescents with borderline personality disorder with the use of quetiapine (Podobnik, Podobnik, Grgic, Marcinko, & Pivac, 2012). In adults, a recent randomized, double-blind, placebo-controlled trial examining effectiveness of extended-release quetiapine for borderline personality disorder has demonstrated reduction of symptoms in those treated with low-dose (150mg daily) quetiapine (Black, Zanarini, Romine, Shaw, Allen, & Schulz, 2014). Quetiapine also has demonstrated utility in certain anxiety disorders (Katzman et al., 2014), and its XR formulation is approved by the FDA for use as an adjunctive agent in major depressive disorder in adults. The anti-anxiety and antidepressant effects of quetiapine may in part be attributed to inhibition of the norepinephrine transporter and its effects on 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors (Ravindran,

Al-Subaie, & Abraham, 2010). Given that the youth prescribed quetiapine in this study were often those with depressive, anxiety, and cluster B personality symptoms, the choice of clinicians to use quetiapine may have been a result of wishing to use a single agent to manage multiple comorbidities in addition to insomnia, potentially avoiding polypharmacy and its inherent risks. Again, careful weighing of risks and potential benefits should be present in the decision making process of prescribing quetiapine.

It seems in most of the cases where quetiapine was used primarily for insomnia, the agent was initiated in hospital, with no documentation of prior trials of sedative agents in the community. This may point to a possible preference for clinicians to use quetiapine acutely in hospital as opposed to on an outpatient basis. It may be that clinicians perceive the potential benefit provided by quetiapine for the treatment of insomnia outweighs its potential risks when used on a short-term inpatient basis. If this were the case, it would be important for the medication to either be discontinued on discharge, or for there to be a clear discontinuation plan in the community. In our study, two-thirds of youth prescribed quetiapine solely for insomnia were prescribed quetiapine on discharge, and it is uncertain in how many of these cases plans for discontinuing quetiapine were discussed with the patient, family, and/or community physician. It would be important to know how long these patients were continued on quetiapine after discharge. Sleep difficulties may be exacerbated in the inpatient setting, and the importance of outpatient monitoring of continued difficulties is critical. If started in hospital, we advocate for clinicians to clearly outline plans for discontinuation of quetiapine, if that is indeed the plan, in their communication with patients, families, and outpatient care providers in order to mitigate adverse long-term effects of continued quetiapine use.

Low doses of quetiapine were used for the treatment of insomnia at our center, and quetiapine was prescribed more often as a routine medication as opposed to on an as needed basis. It is important to note that low dosing cannot be assumed to equate to increased safety. Weight gain has been noted in retrospective studies of adults taking low dose quetiapine, and there have been case reports of serious adverse effects such as fatal hepatotoxicity, RLS, and akathisia also with low-dose use (Coe & Hong, 2012). There is little evidence to support a dose-dependent relationship between quetiapine and metabolic effects (Simon, van Winkel, & De Hert, 2009). That is to say, low dosing cannot be assumed to equate to increased safety.

The risks of using quetiapine need to be weighed with its potential benefits, as improved sleep may have a positive impact on mental health that may outweigh the risks of short-term use. There unfortunately remains few studies examining the effectiveness of quetiapine for insomnia. We did not assess the efficacy or effectiveness of quetiapine as compared to other agents in this study. This would be a very

relevant research question for future study as medications are typically used as a last resort in youth with insomnia, and improved sleep is often important for overall psychiatric symptom improvement.

We found that in cases where quetiapine was prescribed for insomnia, there were concurrent prescription of other sedative agents. This typically occurred when one or more of these agents were ordered by the admitting physician on an order set at the beginning of a patient's admission. These agents may not have been discontinued prior to quetiapine being started, potentially resulting in unnecessary polypharmacy.

Existing sleep treatment guidelines address primary and behavioural insomnias as opposed to insomnias occurring with multiple psychiatric comorbidities or in the acute inpatient setting. Emphasis of these guidelines is placed on trying behavioural interventions first, followed by using melatonin in conjunction with a rigorous sleep hygiene program (Gruber et al., 2014; Cummings & Canadian Paediatric Society, Community Paediatrics Committee, 2012), which certainly can and should be tried in the inpatient setting given the low risk profiles of both. There is little else in terms of other formal medication recommendations within guidelines for children and adolescents, with many sedative agents noted as having potential adverse effects and/or be lacking in evidence for effectiveness (Gruber et al., 2014). It is recommended that for secondary insomnia, trying to choose an agent (such as a sedating antidepressant in the case of depression) to tackle both primary psychiatric illness and resultant insomnia may be helpful (Gruber et al., 2014). In any case, there continues to be consensus that antipsychotics such as quetiapine are not to be used as a first line agent in the treatment of insomnia in children and adolescents.

There are certain limitations to our study. We chose to examine our data by admission as opposed to by patient, and thus some admissions involved the same patient (i.e. in cases where a patient was admitted more than once to the unit in 2013). We also did not examine the demographic data of all patients admitted to the unit in 2013 as a comparator to our group of patients prescribed quetiapine for insomnia, limiting our ability to draw clear conclusions about our clinicians' potential preferential prescribing of quetiapine to certain youth. The discharge diagnoses of each admission were obtained through informal discharge sheets completed by clinicians at the time of discharge, which sometimes contain, in our hospital setting, provisional diagnoses. A more accurate way of recording patient diagnoses would have been to record diagnoses described in formal dictated discharge summary reports. As well, we did not differentiate between primary diagnoses responsible for admission and contributing comorbidities. Additionally, we were only able to infer the intentions behind clinicians' prescriptions based on what was recorded in the chart. In practice,

decision making behind these prescriptions is often more complex with perhaps additional reasons for why a medication is chosen than what is documented. While we looked at medication orders through our chart reviews, we did not access pharmacy records to examine what was actually administered; thus, we were unable to determine whether, and if so for how long, other sedative agents were administered prior to quetiapine use, and whether concurrently prescribed sedative agents were jointly administered within the same time frame. As well, we did not stratify prescribing practices based on individual clinicians to see if the tendency to use quetiapine for insomnia was true for particular clinicians or generally for our clinicians as a group. In addition to the data we gathered, it would have been helpful to know in how many patients behavioural interventions were tried before the use of pharmacotherapy, and whether metabolic parameters such as weight were recorded before and after the start of quetiapine. As well, it is interesting to consider how often clinicians prescribe medications for insomnia on an inpatient unit in general; this would be an important topic for future research and may be related to sleep disturbances in refractory psychiatric illnesses.

Conclusion

Quetiapine was found to be used not uncommonly for insomnia in our inpatient child and adolescent psychiatric unit (for insomnia only in 6.5% of all 2013 admissions, and for insomnia jointly with another reason in 2.9% of all 2013 admissions). Most of those prescribed quetiapine solely for the documented reason of insomnia were females and those with anxiety, eating disorders, borderline personality disorders or Cluster B traits, and depressive disorders, though it is unclear whether this was a deviation from the admitted population as a whole in our year of study. While there is little data for quetiapine as a treatment of insomnia, particularly as a first-line agent, our study suggests that the prescribing of sedative agents within the time-limited setting of an inpatient unit may be more nuanced than at first glance. Careful weighing of risks and benefits is essential.

It is important for clinicians to be aware of the evidence or lack of evidence while using quetiapine, consider comorbidities, and document clearly all rationales for its use. Trying behavioural interventions and melatonin first, and reserving quetiapine as a later agent for treating insomnia, is recommended if possible, remembering also to discontinue previously trialed sedative agents as new ones are prescribed to prevent polypharmacy. We recommend clinicians discuss the sleep management approach collaboratively with patients and their families. Finally, while the inpatient setting may be a particularly unique setting in which to consider use of quetiapine, this medication was prescribed or recommended as a medication for use upon discharge. It is essential for clinicians to actively communicate plans for its intended short-term use, if that is the case, to patients, families, and their community physicians so as to limit long

term exposure and mitigate consequent serious metabolic and other risks to patients.

Acknowledgements / Conflicts of Interest

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