

**Medicines Adverse Reactions Committee**

Meeting date	<b>3 July 2018</b>	Agenda item	3.2.2
Title	<b>Atypical antipsychotics and sleepwalking/sleep-related eating disorder</b>		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
<b>Active constituent</b>	<b>Medicine</b>	<b>Sponsors</b>	
Amisulpride	Solian	Sanofi-Aventis	
	Sulprix	Mylan	
Aripiprazole	Abilify	Pharmacy Retailing	
	Aripiprazole Sandoz	Novartis	
Clozapine	Clopine	Douglas Pharmaceuticals	
	Clozaril	Mylan	
Olanzapine	Olanzapine DRLA	Dr Reddy's	
	Zypine	Mylan	
	Zyprexa	Eli Lilly	
Paliperidone	Invega	Janssen-Cilag	
Quetiapine	Auro-Quetiapine	Aurobindo Pharma	
	DP-Quetiapine	Douglas Pharmaceuticals	
	Quetapel	Mylan	
	Quetiapine DRLA	Dr Reddy's	
	Seroquel	AstraZeneca	
Risperidone	Ridal	Douglas Pharmaceuticals	
	Risperdal	Janssen-Cilag	
	Risperidone DRLA	Dr Reddy's	
	Risperidone (Teva)	Teva Pharma	
	Risperon	Mylan	
Ziprasidone	Zeldox	Pfizer	
	Zusdone	Douglas Pharmaceuticals	
Funding	All of the above active constituents have a funded brand with the exception of paliperidone. The special authority criteria for aripiprazole was removed on 1 June 2018.		
Previous MARC meetings	Atypical antipsychotics and sleepwalking/sleep-related eating disorder has not been discussed previously.		
International action	Health Canada <ul style="list-style-type: none"> <li>– In September 2017, Health Canada issued a safety review on the potential risk of sleepwalking and sleep-related eating disorder associated with atypical antipsychotics. Based on this review, Health Canada has recommended updating the product safety information for all atypical antipsychotics to include these adverse effects.</li> </ul>		

Schedule	Prescription medicine
2016 Usage data (dispensed in a community pharmacy, from DataPharm beta)	<p>Amisulpride: 6122 prescriptions dispensed to 1287 people</p> <p>Aripiprazole: 14191 prescriptions dispensed to 3534 people</p> <p>Clozapine: 36455 prescriptions dispensed to 4297 people</p> <p>Olanzapine: 83533 prescriptions dispensed to 17032 people</p> <p>Paliperidone: 10355 prescriptions dispensed to 2754 people</p> <p>Quetiapine: 225435 prescriptions dispensed to 58847 people</p> <p>Risperidone: 85138 prescriptions dispensed to 19266 people</p> <p>Ziprasidone: 2043 prescriptions dispensed to 465 people</p>
Advice sought	<p><b>The Committee is asked to advise:</b></p> <ul style="list-style-type: none"> <li>– On the strength of the evidence for a potential association between each atypical antipsychotic and: <ul style="list-style-type: none"> <li>○ sleepwalking</li> <li>○ sleep-related eating disorder</li> </ul> </li> <li>– Whether any updates to data sheets are required either as a class effect or for individual products</li> <li>– If further communication, outside of MARC's Remarks in <i>Prescriber Update</i>, is needed.</li> </ul>





and that product information for all atypical antipsychotics should be updated to include these side effects.

The purpose of this paper is to review the evidence for these safety signals and obtain MARC's advice on whether any updates to these products are required.

## **2.0 BACKGROUND**

### **2.1 Atypical Antipsychotics**

Antipsychotics are medicines commonly used to reduce symptoms associated with psychotic conditions such as bipolar disorder, psychotic depression, schizophrenia and other psychoses. Due to their sedative properties, some are also used off-label as sleep-aids. Atypical antipsychotics are the group of antipsychotics that includes second-generation antipsychotics. Atypical antipsychotics differ from typical antipsychotics (first-generation) in that they have a more favourable safety profile. They are shown to have a lower risk of extra-pyramidal side effects, however they may pose a greater risk of side effects such as diabetes and weight gain (1).

All antipsychotics have varying effects on serotonergic, dopaminergic and adrenergic pathways. The primary target is the D<sub>2</sub> receptors in the mesolimbic pathway as these are believed to be responsible for positive symptoms of schizophrenia. Antipsychotics are antagonists at these receptors throughout the brain, however atypical antipsychotics are more selective for mesolimbic receptors which give them their different safety profile. Action at D<sub>2</sub> receptors elsewhere in the brain are the cause of many of their side effects, including hyperprolactinaemia (tuberoinfundibular pathway) and extrapyramidal symptoms (nigrostriatal pathway). Other types of dopamine receptors are also believed to be affected by antipsychotics (1).

Unlike typical antipsychotics, atypicals are also postulated to have effects at the 5-HT<sub>2A</sub> receptor. Antagonism at this receptor acts as a "dopamine brake" which reduces the effect of D<sub>2</sub> antagonism at non-target receptors in the nigrostriatal and tuberoinfundibular pathways. This reduces the risk of developing serious side effects such as the ones described previously. Furthermore, 5-HT<sub>2A</sub> antagonism blocks the serotonergic excitation of cortical pyramidal cells, which in turn lowers the activity of hyperactive dopaminergic receptors in the mesolimbic pathway. Other serotonergic receptors are also believed to be involved with the pharmacology of atypical antipsychotics, including 5-HT<sub>1A/1B</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>7/6</sub> (1).

Other receptors are also believed to be affected by atypical antipsychotics, including histaminergic, cholinergic and adrenergic receptors. Affinity towards the different types of receptors yield different side effect profiles for different antipsychotics. Table 1 outlines binding profiles for the New Zealand approved and marketed atypical antipsychotics.

**Table 1: Antagonist binding profiles of atypical antipsychotics approved for use in New Zealand (2)**

<i>Drug</i>	<i>D<sub>1</sub></i>	<i>D<sub>2</sub></i>	<i>D<sub>3</sub></i>	<i>D<sub>4</sub></i>	<i>5-HT<sub>1A</sub></i>	<i>5-HT<sub>1B</sub></i>	<i>5-HT<sub>2A</sub></i>	<i>5-HT<sub>2c</sub></i>	<i>5-HT<sub>6</sub></i>	<i>5-HT<sub>7</sub></i>	$\alpha_1$	$\alpha_2$	<i>M<sub>1</sub></i>	<i>M<sub>3</sub></i>	<i>H<sub>1</sub></i>
<i>Amisulpride</i>	-	++++	++++	-	-	-	-	-	-	++	-	+	-	-	-
<i>Aripiprazole</i>	+	++++(PA)	+++ (PA)	+(PA)	+++ (PA)	+	+++	++(PA)	+	+++ (PA)	++	+	-	-	++
<i>Clozapine</i>	++	++	++	+++	++(PA)	++	++++	++++	+++	+++	++++	+++	++++	+++	++++
<i>Olanzapine</i>	+++	+++	+++	+++	+(PA)	++	++++	+++	+++	++	++	++	++++	++++	++++
<i>Paliperidone</i>	++	+++	+++	++	+(PA)	+++	++++	+	-	++++	+++	+++	-	-	+++
<i>Quetiapine</i>	+	++	++/+	+	++(PA)	+	+	+	++	+++	++++	+++	++	+++	++++
<i>Risperidone</i>	+	+++	++	+++	+(PA)	++	++++	++	-	+++	+++	++	-	-	++
<i>Ziprasidone</i>	+++	+++	+++	+++	+++ (PA)	+++ (PA)	++++	+++ (PA)	++	+++	+++	++	-	-	++

**Legend**

- Clinically insignificant
- + Low
- ++ Moderate
- +++ High
- ++++ Very High
- PA Partial Agonist

## 2.2 Sleepwalking and sleep-related eating disorder

Sleepwalking (SW), which is synonymous with somnambulism, is a behaviour disorder that originates during sleep and results in walking or performing other complex behaviours while asleep. This includes eating while in a somnambulistic state, which is termed sleep-related eating disorder (SRED). More broadly, SW and SRED can be classified under the umbrella term of sleep disorders belonging to the parasomnia family. The major risk associated with SW and SRED is the potential for events such as falls, cooking-induced harm, and potentially driving while asleep (3). Episodes of sleepwalking can also be embarrassing/traumatic for the patient and affect people they may live with, including roommates, family and spouse.

The estimated lifetime prevalence of sleepwalking in the general population is around 7%. The current prevalence rate – within the last 12 months – is significantly higher in children (5%) than adults (1.5%) (4).

Sleepwalking generally occurs in deep non-rapid eye movement (NREM) sleep, stages 3 and 4. These stages are also known as slow wave sleep and typically occur in the first third of the night (3). The pathophysiology of sleepwalking is largely unknown. Several serotonin receptors are involved with the regulation of sleep and muscle movement. It has been hypothesized that dysregulation of central serotonergic activity may be a cause of sleepwalking by increasing slow wave sleep and inducing partial arousal (5). Antagonism at serotonin receptors by atypical antipsychotics may be a cause of such dysregulation. This does not occur with typical antipsychotics (first generation), as they do not exhibit binding to serotonin receptors like atypical antipsychotics do.

The treatment for sleepwalking is identification and removal of the cause, or improving sleep habits. In cases where the frequency of events are high, a low dose benzodiazepine or tricyclic antidepressant may be effective (3).

## 2.3 Data sheets

### 2.3.1 New Zealand

Table 2 summarises the current statements and ADR listings for sleepwalking and SRED in the data sheets for approved antipsychotics in New Zealand.

**Table 2: Wording in New Zealand data sheets for approved atypical antipsychotics in regards to SW and SRED**

<b>Amisulpride</b>	
Solian	None
Sulprix	None
<b>Aripiprazole</b>	
Abilify	Adverse Events During Premarketing-Rare - <i>Sleepwalking and Sleep disorders</i>
Aripiprazole Sandoz	Adverse Events During Premarketing-Rare - <i>Sleepwalking and Sleep disorders</i>
<b>Clozapine</b>	
Clopine	None
Clozaril	None
<b>Olanzapine</b>	
Zyprexa	None
Zypine	None
Olanzapine DRLA	None

<b>Paliperidone</b>	
Invega	<2% Reported in Clinical Trials - <i>Sleep disorder</i>
<b>Quetiapine</b>	
Quetapel	4.8-Rare - <i>Somnambulism and related disorders</i>
Auro-Quetiapine	4.8-Rare - <i>Somnambulism and related disorders</i>
DP-Quetiapine	None
Quetiapine-DRLA	4.8-Rare - <i>Somnambulism and related disorders</i>
Seroquel	4.8-Rare - <i>Somnambulism and related disorders</i>
<b>Risperidone</b>	
Ridal	<1% Reported in Clinical Trials - <i>Sleep disorders</i>
Risperdal	<1% Reported in Clinical Trials - <i>Sleep disorders</i>
Risperon	<1% Reported in Clinical Trials - <i>Sleep disorders</i>
Risperidone-DRLA	<1% Reported in Clinical Trials - <i>Sleep disorders</i>
Risperidone (Teva)	<1% Reported in Clinical Trials - <i>Sleep disorders</i>
<b>Ziprasidone</b>	
Zeldox	Adverse Effects - Rare - <i>Somnambulism</i>
Zusdone	Adverse Effects - Rare - <i>Sleepwalking</i>

**Comments:**

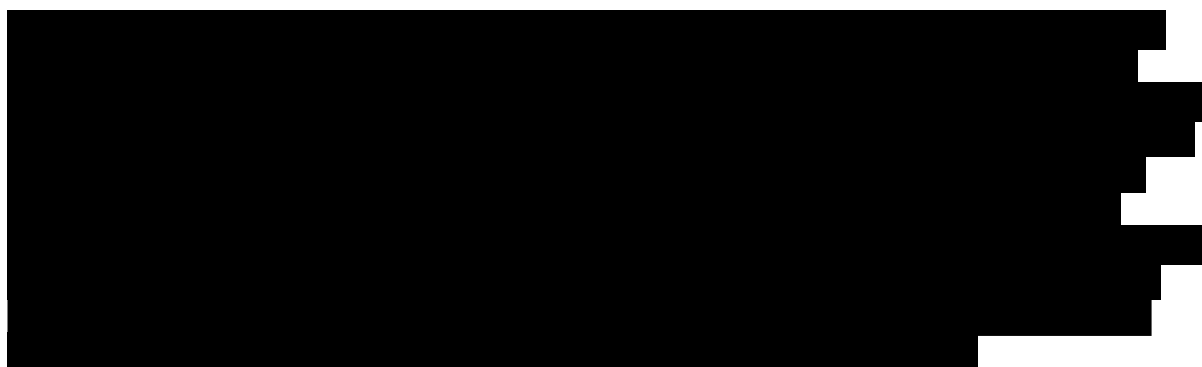
Information in New Zealand data sheets varies and is not consistent across all atypical antipsychotics. Sleep-related eating disorder is not listed in any data sheets. Sleep disorders are listed in some data sheets, however it is not clear whether this encompasses sleepwalking and sleep-related eating disorder or not.

**2.3.2 Australia**

The Australian product information is identical to that of New Zealand.

**Comments:**

International product information for antipsychotics varies, with the consistency that quetiapine lists *sleepwalking and related disorders* as an adverse reaction. Only Canada (see section 3.1) currently has a blanket statement for all atypical antipsychotics. However, it should be noted that the TGA are currently reviewing this topic and changes to their data sheets may be made in the future.

**3.0 SCIENTIFIC INFORMATION****3.1 Health Canada review**





## 3.2 Published Case Reports

### 3.2.1 Faridhosseini F & Zamani A. 2011 (6)

This report describes a 42-year-old male who was prescribed 20 mg olanzapine during an admission to hospital; this was increased from an initial 5 mg dose following a switch from haloperidol. Three months after discharging, reports of sleepwalking with open eyes and loud talking were given by his wife. The patient had no memory of the events the next day. He was relatively functional and schizophrenic symptoms were absent. He had no personal or family history of somnambulism. There was no history of alcohol, nicotine, or other illicit drugs. The olanzapine dose was decreased to 15 mg and clonazepam 1 mg at night was prescribed. Following this change, no further events were reported during 6 months of follow up.

#### *Author(s) comments*

Atypical antipsychotics may increase slow wave sleep via blockade of 5-HT<sub>2C</sub> receptors. This has been postulated to lead to sleepwalking. The patient had no previous history of somnambulism, however this may be due to recall bias. Substance use has also been linked to somnambulism, however the history of this was negative.

### 3.2.2 Tamanna S, et al. 2012 (7)

The first case concerns a 51-year-old African American male who presented with complaints of daytime sleepiness, sleepwalking and sleep-eating for more than a year. The patient could not remember any of the events after awakening. His medical history included depression, hypertension and mood disorder. His medications included bupropion, quetiapine, lisinoprol, hydrochlorothiazide and loratadine. Quetiapine was added in 2006 onto bupropion (150 mg twice daily), for depression, at a titrated dose of 150 mg at bedtime. It was not clear when the SRED first started as the patient lived alone until 2011. He was found to suffer from severe sleep apnoea. He was started on BiPAP (Bilevel Positive Airway Pressure) which helped with the sleep apnoea, but his wife reported his SW and SRED as worsening. Quetiapine was stopped and no further reports of SW or SRED were reported during the one year follow up. This was the only change to his medication during this interval.

The second case concerned a 50-year-old African American female with a history of hypertension, asthma, major depressive disorder, migraine and obstructive sleep apnoea. Her medications included verapamil, lisinopril, hydrochlorothiazide, bupropion, venlafaxine, topiramate and quetiapine. Incidents of sleepwalking and SRED were observed and reported by her niece. These episodes occurred 2 to 3 nights per week. Quetiapine had been used over the past four years for depression at a dose of 200 mg daily. She believed the sleepwalking started 6 to 8 months ago. The quetiapine was tapered and stopped and there was no further events during 3 months follow up. There was no other changes to her medicines made during this interval.

*Author(s) comments*

Both patients had important predisposing risk factors for parasomnias. The mechanism for quetiapine induced somnambulism may be explained by the serotonin hypothesis of parasomnia. Quetiapine blocks 5-HT<sub>2A</sub> receptors in the dorsal raphe nucleus which are known to regulate the frequency and amplitude of slow wave sleep. A blockade of serotonergic input by quetiapine can withdraw normal motor inhibition, enabling the person to walk and perform other activities. Similar receptors (5-HT<sub>2C</sub>) are found in the hypothalamus, where quetiapine antagonism can increase appetite, leading to SRED. This could occur from any antipsychotic as all have serotonergic antagonism potential.

**3.2.3 Das P. 2016 (8)**

This report describes a 28-year-old white male with schizoaffective disorder who reported having residual psychotic symptoms (hallucinations and paranoia) while taking ziprasidone 40 mg twice daily. His dose of ziprasidone was increased to 60 mg twice daily to manage his residual psychosis. One month later, this was changed to 40 mg in the morning and 60 mg at night due to complaints of daytime sedation. Three months later, the patient reported having episodes of sleepwalking with SRED during most nights, observed by his girlfriend. He had no recollection of these events. These events started when the dose increase occurred. The events were resolved upon discontinuation of the night time dose, only taking 40 mg in the morning. As a rechallenge and due to insomnia, night time ziprasidone was restarted at 80 mg. Within one week, sleepwalking and SRED occurred. The night time dose was changed to quetiapine 100 mg without further reports of SW or SRED.

**3.2.4 Raja M & Raja S. 2013 (9)**

The first case describes a 59-year-old female with bipolar II disorder who had severe insomnia. She was prescribed quetiapine 25 mg at bed time. The dose was increased to 50 mg after a number of weeks. A few months after initiating quetiapine, she presented with an episode of SW. She had a vague memory of the experience. She described it as dissociative and dream-like. She had no history of events like this. Her dose was reduced to 25 mg and she did not present with further episodes in the 9 months following. Her brother and daughter both suffer from sleepwalking.

The second case describes a 37-year-old male with bipolar II disorder who presented with insomnia and mood instability. He had always been a poor sleeper. He was prescribed oxcarbazepine 300 mg in the morning and 600mg at night, as well as quetiapine 12.5 mg at night. The quetiapine dose was gradually increased to 50 mg. In the mornings, he started noticing objects had been moved and food, plates, and empty glasses in the kitchen. His roommate had observed him walking and eating during the night. He had previous episodes of SW while taking zolpidem 10 mg. He substituted the quetiapine with 25 mg of promethazine and had no further episodes of SW. It was noted it only occurred when on 25 mg or 50 mg of quetiapine, not 12.5 mg.

The third case describes a 53-year-old man with bipolar II disorder. He presented with an episode of agitated depression. He was treated with quetiapine (titrated dose of 300 mg) and valproate (750 mg) at bed time. He had an episode of sleepwalking, which the patient could recall as being in a dream-like state. He had never had an episode like this prior. This was the only episode and no changes were made to his therapy.

The fourth case describes a 75-year-old female with unipolar recurrent depression who presented with a new episode of depression and insomnia. She was treated with escitalopram 10 mg, quetiapine 25 mg at night, and lorazepam 1-2 mg at night. She was also being treated with amitriptyline 10 mg for migraine, manidipine, nebivolol, metformin and fenofibrate. Six months later, she felt she was being touched while asleep and stood up, but recalled not being fully awake. Her recall of the event was imprecise and indistinct. She recalled some hallucinations like she was in a dream. Her husband noticed her standing in the middle of the room, talking, and awoke her. She had no previous episodes of SW or any other parasomnia.

*Author(s) comments*

The causal relationship between quetiapine and SW is almost certain in case 2 since the patient, by himself, set up an open n(A-B-A-B) study design, in which the patient served as his own control, and always associated the doses of 25 and 50 mg of quetiapine with SW. Although the patient was also taking oxcarbazepine, the role of this drug in inducing SW seems absent or negligible because of the clear-cut association between quetiapine doses and SW.

In case 1, the causal relationship is less certain since the patient presented just one episode of SW. However, the suspect of a causal relationship is grounded. The patient had never presented SW in the past and did not present further episodes after the quetiapine dose reduction. She was not assuming any other drug at the time of SW. Her familial history of SW strongly suggests the diagnosis of SW.

In cases 3 and 4, the causal relationship is uncertain since the patients presented just one episode of SW and they continued quetiapine treatment with the same dose.

In all cases, SW did not occur immediately after starting quetiapine treatment. In cases 3 and 4, SW occurred only once, although patients continued quetiapine treatment at the same dosage. This suggests that the etiological link between quetiapine and SW is neither simple nor absolute and that other unknown factors are likely to be necessary in order to elicit the clinical manifestation of such disorder.

**3.2.5 Kolivakis T, et al. 2001 (10)**

The first case describes a 64-year-old male with a 41 year history of schizophrenia. He was switched from risperidone to olanzapine, which was increased over 10 months to 20 mg at night. After 1 week at this dose, he complained of sleepwalking most nights. This was observed by a roommate and he had no recollection of the events. The dose was gradually decreased and he was eventually switched back to risperidone. Even at low doses of olanzapine, the sleepwalking persisted. However, when the olanzapine was ceased, the events stopped immediately. He had no previous or family history of somnambulism or other parasomnias.

The second case describes a 62-year-old woman with a 35 year history of schizophrenia, treated with loxapine. Olanzapine was added and titrated to a dose of 20 mg at night. At this dose, she reported sleepwalking for 6 months. The events persisted as the dose was tapered and ceased when switched to risperidone.

*Author(s) comments*

Olanzapine significantly increased slow-wave sleep which is the period in which sleepwalking may occur. Antagonism of 5-HT<sub>2C</sub> receptors is believed to increase slow wave sleep.

**3.2.6 Heathman J, Neal DW & Thomas CR. 2014 (11)**

This case describes a 48-year-old female who had been diagnosed with rapidly cycling bipolar disorder 33 years prior. She had been previously treated with multiple mood stabilizers and antipsychotics including risperidone, aripiprazole, ziprasidone, lithium, carbamazepine and valproate. The patient was switched to quetiapine at a titrated dose of 100mg at night. Within 2 days of starting the 100 mg dose, the patient began noticing food throughout the kitchen and dining room in the mornings. Her spouse observed her doing this on subsequent nights. There was also concern that she may attempt to drive to the store as one night she was found holding car keys. Quetiapine was discontinued and had no further reoccurrences of such events.

*Author(s) comments*

The patient had no prior or family history of any sleep-related disorders. She had no other risk factors for sleep disorders.

### 3.2.7 Deng S, et al. 2017 (12)

This case describes a 47-year-old female who developed nightly sleepwalking during treatment with oxazepam, trihexyphenidyl, and concomitant administration of olanzapine and propranolol.

The woman, who was diagnosed with paranoid schizophrenia, was hospitalised in a psychiatric ward. Subsequently, her treatment was started with risperidone 2–6 mg per day. However, she developed extrapyramidal adverse effects secondary to the therapy. Therefore, risperidone therapy was discontinued. Thereafter, she was started on olanzapine 20 mg/night, which was later adjusted to 10mg twice a day. She also started receiving oxazepam 30 mg at bedtime for insomnia and trihexyphenidyl 2 mg twice a day for extrapyramidal adverse effects. After three weeks of olanzapine therapy, she complained of akathisia. Hence, propranolol 10 mg twice a day was added to the treatment regimen. The same night of the treatment, the nursing staff reported that she was walking around in the ward within two to three hours after falling asleep. The next day, she was unable to recall the event. Consequently, her olanzapine dose was adjusted to 10 mg per day, and propranolol was continued at the same dose. However, her SW recurred. After the second SW incident, the woman's olanzapine therapy was discontinued, though propranolol therapy was continued at the same dose. Quetiapine and aripiprazole were added to her treatment regimen. Thereafter, she had good compliance to the therapy of quetiapine, aripiprazole, propranolol, oxazepam and trihexyphenidyl. Recurrence of SW was not noted during the following three months.

#### *Author(s) comments*

It was considered that her SW was due to the concomitant administration of olanzapine and propranolol, with possible contribution by oxazepam and trihexyphenidyl. Co-administration of olanzapine and propranolol is possibly the precipitating factor in the patient's SW history. We cannot rule out other drug effects such as oxazepam and trihexyphenidyl.

### 3.2.8 Das S, et al. 2017 (13)

This case describes a 26-year-old man who developed somnambulism during therapy with olanzapine. The man, who had a two year history of schizophrenia, presented with symptomatic exacerbation. He was hospitalised and was given haloperidol with promethazine for two days due to acute agitation and violent behaviour. Afterwards, he was switched to oral olanzapine from the third day along with lorazepam. Initially, he received oral olanzapine 5 mg per day, which was later increased by 5 mg every ten days. Two weeks after admission, his psychotic symptoms improved. However, at the dose of 15 mg/kg day, he had abnormal behaviour during sleep. He would get up, walk in the ward, and try to pull the pillows and bed sheets of other patients. He would also bang his head against walls. He also tried to throttle other patients on two occasions. He used to sleep after each episode and had complete amnesia of the events on awakening. Subsequently, he was diagnosed with sleep walking.

The man's olanzapine was gradually reduced to dose of 5 mg per day and clonazepam was added in the treatment. This led to resolution of his symptoms. A week later, dose of olanzapine was again increased to 15 mg per day because of his worsened psychotic symptoms. After three to four days, his sleep walking reappeared. Thus, his olanzapine was cross tapered with aripiprazole under clonazepam cover. Later, his symptoms did not recur with aripiprazole and he was discharged, two months after clinical stability.

#### *Author(s) comments*

The resolution of SW after decreasing olanzapine and its relapse after reintroduction in this case confirms the role of olanzapine (15 mg per day) in precipitating sleepwalking episodes.

### 3.2.9 Baumgartner J, Schmauss M & Stubner S. 2016 (14)

This case describes a 50-year-old man who developed somnambulism while receiving olanzapine. The man started receiving therapy with olanzapine at a dosage of 20 mg per day for schizoaffective

disorder. The dose of olanzapine was subsequently increased to 25 mg per day. Two days later, an episode of somnambulism occurred with short-term confusion, disorientation, fidgeting and subsequent amnesia regarding the events. Another episode occurred the following night. One hour later, he presented to the hospital in a completely orientated state, but could not recall the earlier event. The dose of olanzapine was reduced to 20 mg per day, 5 days later. After 2 days, he availed himself of weekend leave and returned to the hospital at night by ambulance. His wife reported that he woke up sweating and again appeared to be confused. Olanzapine was tapered to discontinuation. During the following nights, no further episodes of somnambulism were noted.

### **3.2.10 Dagan Y & Katz G. 2013 (15)**

This case describes a man in his 40s who developed somnambulism following treatment with olanzapine, quetiapine and asenapine. The man, whose history included bipolar disorder, developed sleepwalking episodes in August 2000 after olanzapine 15 mg per day was added to his treatment with lithium. He developed similar episodes after quetiapine 600 mg per day was added to his treatment with carbamazepine and valproate. His sleepwalking subsided after discontinuation of the antipsychotic drug in both cases. A year later, in November 2011, he was hospitalised with a manic episode at the age of 52 years. Asenapine was started in the emergency department and increased gradually to 15 mg per day over 2 weeks. He was observed sleepwalking after 2 weeks on this dose. At the man's request, asenapine was withdrawn. His sleepwalking stopped.

### **3.2.11 Seeman MV. 2011 (16)**

This case describes a 50-year-old woman who had a history of schizophrenia since her early 20's and was receiving quetiapine, titrated to a dosage of 800 mg per day and sertraline 200 mg per day for co-morbid depression. She subsequently reported that someone was breaking into her apartment at night, as her household items were being displaced overnight. Her quetiapine dosage was increased to 900 mg per day on the suspicion of delusional thoughts. However, she started to report that she had been sleepwalking. A diagnosis of sleepwalking was supported by somnography results. She received clonazepam, and she did not report any further episodes of sleepwalking.

### **3.2.12 Chiu Y, Chen C & Shen W. 2008 (17)**

This case describes a 52-year-old man with no history of sleep disorders who developed somnambulism, while receiving olanzapine for bipolar I disorder. The man was initiated on olanzapine 5 mg per day at bedtime during a manic episode, and titrated up to 20 mg per day over 10 days. He was also receiving lithium and valproic acid. Six days after reaching 20 mg per day of olanzapine, he started walking around within 2 to 3 hours of going to sleep. This would occur intermittently, and would sometimes involve lying on the ground or urinating beside his bed, with no memory of the episode the following day.

The dose of olanzapine was reduced to 15mg at bedtime. The frequency of somnambulism decreased and he was discharged, also maintained on valproic acid and lithium. Although less frequent, the somnambulatory behaviour continued, and 2 months later after a further episode, he ceased his olanzapine altogether. The somnambulism subsequently ceased. At last follow-up he was continuing to receive lithium and valproic acid, and was doing well.

#### *Author(s) comments*

Regarding the chronology of the symptoms, somnambulism in our case appeared clearly related to adding olanzapine to the patient's treatment and disappeared after discontinuing olanzapine. Thus, we suggest that olanzapine is possibly the cause for our patient's somnambulism.

### **3.2.13 Hafeez Z & Kalinowski C. 2007 (18)**

Two patients developed somnambulism while receiving quetiapine; the first patient's symptoms were aggravated while receiving concomitant mirtazapine.

A 52-year-old man had panic disorder, schizoaffective disorder, restless legs syndrome and attention-deficit hyperactivity disorder (ADHD). He received quetiapine 50 mg at bedtime for 2.5 months. The dose was increased to 100 mg for 2 days, then increased further to 200 mg, and continued at this dose for 9 months. After the increase to 200 mg, he developed somnambulism. Eighteen months after somnambulism began, he was admitted to a medical unit after falling off his porch while sleepwalking. The previous month, quetiapine had been titrated to 1000 mg nightly. He was also receiving mirtazapine 30 mg at bedtime during this period, which further aggravated his somnambulism. He would wander in a confused state, manipulate belongings, eat and visit the bathroom. Quetiapine was discontinued, and his somnambulism stopped. Quetiapine was restarted at a dose of 25 mg nightly for anxiety and insomnia. At 8-month follow-up, somnambulism had not recurred.

An 18-year-old boy had pervasive developmental disorder, oppositional defiant disorder and ADHD. He started receiving quetiapine for command auditory hallucinations caused by stimulant medication. Soon after, he started to have nocturnal episodes of jumping from his bed, shouting, property destruction, assaults on family members and attempts to climb walls. He woke in the mornings with a headache but no recollection of events. Eight months after quetiapine initiation, he sought consultation. At this time, he was receiving quetiapine 400 mg nightly. Quetiapine was decreased to 350 mg nightly. His nocturnal outbursts became less frequent and less intense. Quetiapine was tapered to 50 mg over several months. Below a dose of 150 mg nightly, his nocturnal outbursts resolved. Quetiapine was discontinued. After 1 year, he had no recurrence of somnambulism.

### **3.2.14 Lu M & Shen W. 2004 (19)**

This case describes a 68-year-old man who developed a sleep-related eating disorder during treatment with risperidone for psychotic symptoms associated with vascular dementia. The man received risperidone 1 mg per day for 1 month, but his psychotic symptoms persisted and his risperidone dose was increased to 2 mg per day. His psychotic symptoms gradually resolved, but he developed sleep disturbances, with episodes of somnambulism most nights, during which he ate large amounts of food; he had no memory of the episodes upon waking. After 2 months the man's risperidone dose was decreased to 1 mg per day and his sleep-related eating disorder quickly resolved.

#### *Author(s) comment*

Risperidone, which is known to have potent dopamine D<sub>2</sub> and serotonin 5-HT<sub>2</sub> antagonistic properties, has the potential to increase the slow-wave sleep period. One study suggested that the decrease in dopaminergic and/or serotonergic activity might contribute to SRED.

### **3.2.15 Paquet V, et al. 2002 (20)**

This case describes a 52-year-old man with a family history of sleepwalking who developed a sleep-related eating disorder during olanzapine treatment for bipolar I disorder. After presenting with an episode of mania and psychomotor agitation, olanzapine 10 mg per day was added to the man's existing medication regimen which included lithium. At a routine follow-up visit, he reported sleep disturbances that occurred most nights and had started several days after olanzapine was started. When asleep, he walked through his apartment and ate large amounts of sweet food. When his wife tried to wake him he became aggressive. In the morning he had no recollection of his behaviour. Olanzapine was discontinued and the man's sleep-related eating disorder rapidly disappeared with no subsequent recurrence.

#### *Author(s) comment*

Regarding the chronology of the symptoms, the occurrence of SRED in this case appears clearly related to the addition of olanzapine to the treatment of our patient.

Comments

Reports are primarily of quetiapine (n=12) but include other antipsychotics also. This may be due to the comparatively higher prevalence of quetiapine use. Olanzapine also had a high number of published reports (n=8). Most case reports presented a positive de-challenge and one case had a positive re-challenge. It appears the effect is dose-related as it often occurred following dose increases and in some cases reduced in frequency after a dose reduction(s).

Many of the cases had potential confounding factors such as various mental disorders, concomitant medicines, family history of SW or a history of other sleep disorders. However, the association of SW occurrence and events such as dose increases and drug initiation, alongside positive de-challenge, supports the hypothesis that this is a drug related adverse reaction to atypical antipsychotics. Some authors also suggest biological plausibility in their comments.

Although a number of atypical antipsychotics have been associated with SW and SRED in case reports, an intra-patient class-effect is not typically seen, as shown by events ceasing after switching to a different atypical antipsychotic. This implies other intrinsic factors may be necessary to produce this adverse reaction, such as varying patient sensitivity to different antipsychotics.

### 3.3 Company reports

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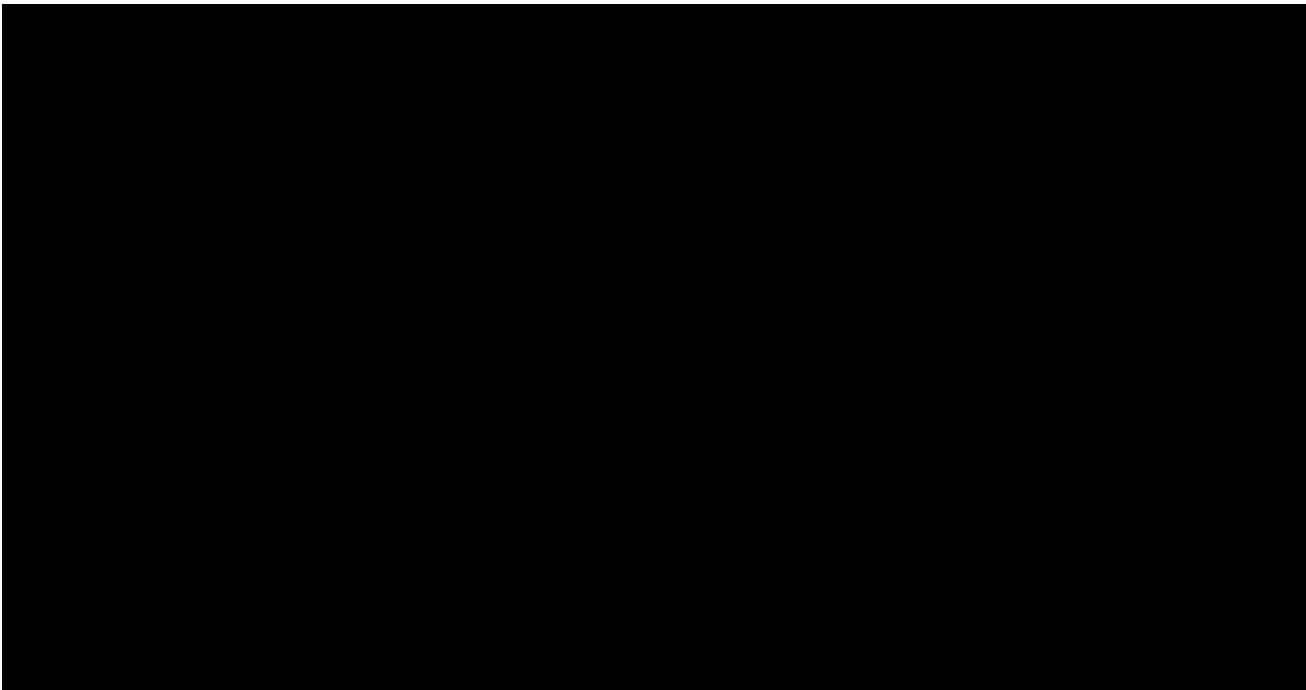
### 3.4 Post-marketing reports

#### 3.4.1 Centre for Adverse Events Monitoring (CARM)

CARM has not received any cases with any atypical antipsychotic pertaining to sleepwalking or sleep-related eating disorder up to 31 March 2018.

[REDACTED]

[REDACTED]



[Redacted text block]

**3.4.6 World Health Organisation (WHO)**

The WHO database, VigiBase, contains 436 individual case safety reports (ICSRs) of an atypical antipsychotic pertaining to sleepwalking (preferred term) and/or sleep-related eating disorder (preferred term). The search included some atypical antipsychotics that are not available in New

Zealand, such as lurasidone, asenapine and loxapine. These reports were not assessed for causality due to the large volume of reports.

The WHO uses a numerical value for detecting signals called the Information Component (IC). This is an indicator value for the disproportionality of reporting. The lower end of a 95% confidence intervals for this, IC<sub>025</sub> are also calculated as part of their signal detection. An IC value greater than one with a positive IC<sub>025</sub> indicates a potential signal.

Table 7 shows the drug-event associations that are potential signals according to VigiBase reports.

**Table 7: Information Components of drug-event associations that are potential signals according to UMC criteria**

Substance	Reaction (PT)	IC025	IC
Quetiapine	Sleep-related eating disorder		
Quetiapine	Somnambulism		
Asenapine	Somnambulism		
Ziprasidone	Somnambulism		
Olanzapine	Somnambulism		
Aripiprazole	Somnambulism		
Ziprasidone	Sleep-related eating disorder		
Aripiprazole	Sleep-related eating disorder		
Olanzapine	Sleep-related eating disorder		

#### Comments

227 reports of somnambulism and 66 reports of sleep-related eating disorder were for quetiapine. For each of the adverse reactions, quetiapine is largely the most commonly reported suspect medicine. Whether this is related to the frequency of its use in relation to other atypical antipsychotics or for other reasons is unknown. However, other atypical antipsychotics are also implicated, leading to the hypothesis that this may be a class effect rather than solely a signal for quetiapine.

The IC values in table 7 indicate a number of potential medicine-ADR signals with a variety of atypical antipsychotics and both SW and SRED. This can be viewed as evidence for a possible class-effect alongside the biological plausibility and published case reports presented elsewhere in this paper.


## 4.0 DISCUSSION AND CONCLUSIONS

Although there have been no reports in New Zealand of SW or SRED with atypical antipsychotics, the number of reports globally justifies this association as a potential signal. Statistical analysis of the reports in the WHO's VigiBase supports the signal, as the number of reports is higher than expected. These events are likely to be underreported as the patient may be unaware; of note in many of the case reports above the events were first noticed by a partner or roommate.

The utilization of different atypical antipsychotics varies, which causes bias towards increased reporting for the more commonly used medicines. However, the evidence appears to be strongest for quetiapine followed by olanzapine. Somnambulism and related disorders are listed in the quetiapine data sheets, but not in any for olanzapine. However, as there are reports of these events with many different atypical antipsychotics consideration should be given to the class as a whole. Data sheets for aripiprazole and ziprasidone list somnambulism or sleepwalking as an adverse effect, despite the lower number of reports.

Evidence for the association being a class effect is supported by biological plausibility. The proposed mechanism, interruption of cortical serotonergic pathways, could occur with any atypical antipsychotic, as they all have some degree of antagonist/partial agonist binding to various serotonin receptors in the central nervous system. This is hypothesized to increase slow wave sleep, the stage of sleep where sleepwalking generally occurs. However, there are likely to be intrinsic factors that are also important in the development of the adverse effect, as observed by patients successfully switching to different atypical antipsychotics and achieving cessation of SW/SRED events.

The association is further supported by 21 published case reports of such events with patients taking atypical antipsychotics. The authors' conclusions in these reports were generally that the adverse effects were caused by the atypical antipsychotic. The case reports provide strong evidence of association due to positive de-challenge and also show that it is likely a type-A adverse effect (dose-related).



With the higher than expected number of spontaneous reports, biological plausibility and strong evidence presented in the case reports in the literature it seems likely that atypical antipsychotics may induce sleepwalking and sleep-related eating disorder in some patients. Sleepwalking and sleep-related eating has the potential to cause harm, particularly if this is mistaken for a relapse in the patient's condition. Highlighting this effect in the data sheet if the Committee agrees there is an association would therefore be helpful. Proposed below is examples of potential wording that could be considered for inclusion in New Zealand data sheets:

**Section 4.8**

*Psychiatric – Rare/Post Marketing*

*Somnambulism and related disorders such as sleep-related eating disorder*

Or

**Section 4.4**

*Risk of somnambulism (sleepwalking) and sleep-related eating disorder have been associated with the use of atypical antipsychotics including [medicine]*

## 5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- On the strength of the evidence for a potential association between each atypical antipsychotic and:
  - sleepwalking
  - sleep-related eating disorder
- Whether any updates to data sheets are required either as a class effect or for individual products
- If further communication, outside of MARC's Remarks in *Prescriber Update*, is needed.

## 6.0 ANNEXES

1. Mylan Review
2. AstraZeneca Review [confidential]
3. MSD Review [confidential]

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