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Safety and Usage of Atypical Antipsychotic Medicines in Children

A Nationwide Prospective Cohort Study

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Abstract

Objective: To study the safety and usage of atypical antipsychotic medicines in post-marketing use in a nationwide paediatric population.

Design: Prospective observational cohort study using prescription event monitoring and record linkage.

Population: New Zealand children aged ≤15 years, who were prescribed atypical antipsychotic medicines between April and July 2003.

Outcomes: Usage measures included prescription data for each medication, the diagnosis for which the patient was being treated and main target symptom. Safety outcome measures were all new clinical adverse events between the start of treatment (which could be before April 2003) and 30 November 2004.

Results: The cohort included 420 children aged 2–15 years. Total exposure to atypical antipsychotic medicines was 641.2 patient-years of treatment with most (94%) of the exposure being to risperidone. The most common diagnoses were disruptive disorders. The symptoms most frequently targeted by the atypical antipsychotic were aggression and difficult behaviour. The treatment of sleep disorders as a target symptom was reported in 3% of children. A total of 131 (31%) children experienced an adverse event. The most frequent adverse events reported were weight gain, severe dental caries and somnolence. The incidence of diabetes mellitus was 4 (95% CI 0.5, 15) cases per 1000 patient-years of treatment in this study. Four children prescribed risperidone developed symptoms of depression, giving an incidence of 8 (95% CI 2.0, 21) cases per 1000 patient-years of treatment.

Conclusions: This study provides a picture of 'real-life' use of atypical antipsychotics in a nationwide cohort of children. Most prescriptions were for risperidone and the most common diagnoses were disruptive disorders. Investigation of the symptoms targeted by these medicines identified unexpected use for the treatment of sleep disorders. Regarding safety, symptoms of depression were identified as a potential new signal for risperidone in the paediatric population. Further research is now required to investigate this.

The number of prescriptions of antipsychotic drugs for children and adolescents increased 6-fold between 1993 and 2003 in the US.[1] The prevalence of the use of atypical (second-generation) antipsychotic medicines has been notably high in this population: one large study reported that 267 per 100 000 commercially insured youths aged ≤19 years received a prescription for these drugs.[2]

Atypical antipsychotic drugs are currently used in the treatment of psychiatric disorders of childhood including schizophrenia, bipolar disorders, pervasive developmental disorders, disruptive behaviour disorders, Tourette's disorder and mental retardation.[3] Whilst a number of reports regarding the use of these drugs in children has been published, most studies have been short-term – usually including small numbers of patients and in select populations – or were case reports.[3] The need for more information on the safety of antipsychotics in children has been recognised for some time. At the US National Institute for Mental Health (NIMH) conference in 2000, a workshop took place 'to improve the methods for long-term assessment of drug-associated adverse effects and advance knowledge of the safety profile of psychotropic medicines in children and adolescents.'[4] This meeting concluded that concerted effort was required to develop systematic research on the long-term safety of psychotropic drugs in children.

In New Zealand, the Intensive Medicines Monitoring Programme (IMMP) is studying the safety of four atypical antipsychotics – clozapine, risperidone, olanzapine and quetiapine. This prospective nationwide study was undertaken to examine the post-marketing safety and usage of atypical antipsychotics in children aged ≤15 years.

Methods

The methodology used by the IMMP has been described in detail previously.[5] Essentially, prescription event monitoring (PEM) is used to undertake prospective observational cohort studies of selected medicines in post-marketing use. Cohorts of patients prescribed monitored drugs are established from prescription data sent directly to the IMMP from pharmacies throughout New Zealand. Information collected from the pharmacy data includes details of the patient, prescriptions dispensed and prescribing doctor.[5] Adverse clinical events are primarily identified from follow-up questionnaires sent to patients' doctors. The IMMP, which is part of the New Zealand Pharmacovigilance Centre, also identifies adverse events from the national spontaneous reporting programme, pharmaceutical companies and from pharmacy data for the monitored drugs.

This 'intensive' methodology has been further enhanced by performing record-linkage between IMMP patient cohorts and national morbidity and mortality databases, in order to identify other adverse events that may have resulted in hospital admission or death.[6] In this study, we employed both routine IMMP follow-up (including spontaneous reporting) and record-linkage to identify adverse events in children taking atypical antipsychotic medicines.

Privacy and Ethical Issues

The processes and practices of the IMMP have been set up to comply with the NZ Health Information Privacy Code and the Privacy Commissioner has been advised of the purpose and methodology of the programme. Details of the privacy and ethical practices of IMMP have been published[7] and are available on request from the IMMP Director (Dr Mira Harrison-Woolrych).

This paediatric study used routine IMMP methodology and, therefore, additional ethical approval was not required. During the study (as is the practice during any of our monitoring studies), questions from doctors or patients regarding privacy and ethical matters were answered directly by the IMMP Director.

Establishing the Cohort

In early 2004, when this study was planned, the IMMP databases included prescription data for all New Zealand patients dispensed a prescription for clozapine, olanzapine, risperidone or quetiapine between 1 April and 31 July 2003. To conduct this paediatric study, we identified all patients aged ≤15

years who had been dispensed a prescription for one of these four drugs during this 4-month period.

Follow-Up

Follow-up was primarily by questionnaires sent to each child's doctor - either the psychiatrist or general practitioner. The questionnaire for this study was based on the routine IMMP questionnaire, in which doctors report all new clinical adverse events that have occurred since patients started treatment with the medication.[6] The IMMP follow-up questionnaires also ask whether the treatment was continued and the reason for treatment cessation if the drug was discontinued.

The paediatric questionnaire was specifically designed for this study and requested the treatment start date (which may have been prior to 1 April 2003) for the atypical antipsychotic drug. The questionnaire also included questions about the diagnosis/indication for use of the atypical antipsychotic, the main symptoms targeted by antipsychotic treatment, the dose once stabilised on treatment and concomitant medications.

The follow-up questionnaires were sent in September 2004 to ensure at least 1 year of follow-up from the latest treatment start date. Reminders were sent in early 2005, but only adverse events occurring before 1 December 2004 were included in the analysis. Thus, the follow-up period for each child in this study was from the treatment start date stated on the questionnaire (or if not stated, the first prescription between 1 April and 31 July 2003) until 30 November 2004 (or the date the medicine was stopped, if prior to this date – see the Analysis section).

Record-Linkage

In New Zealand, there are national morbidity and mortality databases in which hospital admissions and deaths are recorded. Patients can be identified in these databases by their unique National Health Identifier (NHI) number, which is included in IMMP prescription data. It is thus possible to obtain mortality and morbidity data for patients in the IMMP cohorts by record linkage to these databases.[6]

Following verification of the NHI number for each patient, all clinical events listed in the databases occurring before 1 December 2004, were identified. In patients for whom no follow-up questionnaire was returned, an attempt was made to identify the child's diagnosis from these databases.

Clinical Assessment

As for other IMMP studies, the aim was to identify and assess all new adverse clinical events from the time the patient started treatment with the monitored medication.[6] Adverse events identified from all sources were assessed by medically trained staff. Events were coded using terms from a specialised dictionary based on the WHO Adverse Reaction Terminology[8] and causality assessment was performed to determine the relationship with the medication.[9] Events were coded without prejudice: those not considered to have a causal relationship with the drug were classified as 'incidents'[5] whilst others with a definite, probable or possible causality[9] were classified as 'reactions'.

Analysis

For calculation of the patient-months of exposure, the treatment start date was that stated on the follow-up questionnaire, or if not reported, the date of first prescription in the period April–July 2003. The last treatment date was as stated on the questionnaire or the last date from the IMMP prescription data. If the patient continued the medication beyond 30 November 2004, this was taken as the end date. Total patient-months of exposure calculated for each drug included those patients who switched atypical antipsychotic medications or who took more than one atypical antipsychotic drug concomitantly.

For calculation of the cumulative incidence of events, we used two denominators. First, we used the total cohort as the denominator, which was most appropriate for events detected by record-linkage. Second, we calculated the incidence in children with a returned questionnaire, which was appropriate for

events likely to be reported on follow-up questionnaires. The Poisson distribution was used for calculation of the 95% confidence intervals around the estimates of incidence.

Results

Between 1 April and 31 July 2003, 18 442 patients throughout New Zealand were dispensed prescriptions for clozapine, olanzapine, risperidone or quetiapine. From these patients, we identified 424 children aged ≤15 years at the time of first prescription during this 4-month time period. Four patients had no identifiable doctor and were excluded; therefore, the cohort for this study consisted of 420 patients. There were 329 (78%) boys and 91 (22%) girls and the age of patients ranged from 2 to 15 years, with median and mean ages of 10 years.

Medication Prescribed

During the cohort period, 389 (93%) children received a prescription for risperidone, 34 (8%) were prescribed quetiapine, seven (2%) were prescribed olanzapine and one child received clozapine. Eleven children were prescribed two atypical antipsychotics – ten received quetiapine and risperidone and one received quetiapine and olanzapine. By the end of the follow-up period (30 November 2004), 391 patients in the cohort had received a prescription for risperidone, 45 for quetiapine, 11 for olanzapine, two for clozapine and 26 children had been prescribed more than one atypical antipsychotic.

Total exposure to atypical antipsychotic medicines in this study was 7694 patient-months (641.2 patient-years) with the majority (94%) of exposure being to risperidone (table I).

Table I. Treatment durations and total exposure in children aged ≤15 years (n = 420)

Atypical antipsychotic	Mean duration (days)	Median duration (days)	Total exposure (patient-months)
Risperidone	556	539	7252
Quetiapine	215	76	323
Olanzapine	291	214	107
Clozapine	184	184	12
Total			**7694**

Responses to Follow-Up

A total of 430 questionnaires were sent for 420 children in the cohort (ten patients were identified prior to follow-up as receiving prescriptions for two atypical antipsychotics and therefore required two questionnaires). A follow-up questionnaire was returned for 290 of 420 patients, giving a response rate of 69%. Of these, 271 (93%) questionnaires were for patients prescribed risperidone. Fifteen questionnaires were returned blank; therefore, 275 (65%) questionnaires had assessable information.

An NHI number was obtained and verified for all 420 (100%) patients in the cohort, and 120 (29%) were identified as having hospital admissions during the follow-up period. Not all hospital admissions were related to new adverse events; for example, the child may have been admitted for treatment of their underlying condition.

Dosages

The drug dosage was reported for 211 patients (77% of the 275 with assessable questionnaires) of whom 205 were prescribed risperidone. Dosages of risperidone in these patients ranged from 0.1 to 4.5 mg/day, with median and mode dosages of 1 mg/day.

Diagnoses and Target Symptoms

The indication for use/diagnosis was obtained for 265 children (63% of the cohort), with 180 having one diagnosis, 70 having two diagnoses and 15 having no specific diagnosis reported. The results are shown in table II.

At least one target symptom was reported for 208 children (76% of 275 assessable questionnaires). For 134 patients one target symptom was stated and for 74 patients two were reported. Target symptoms were grouped together for analysis (table III).

Adverse Events

A total of 247 reports of adverse events were identified in 131 children (31% of the cohort). Of these, 159 were included in follow-up questionnaires, 84 were identified via record-linkage and

Table II. Diagnoses/indications for atypical antipsychotic use in children aged ≤15 years (n = 265)

Diagnosis (included conditions)	Number of patients[a]	Proportion (%)[b]
Disruptive disorders (conduct disorders, ADHD)	113	43
Pervasive developmental disorders (autism, Asperger's syndrome)	89	34
Cognitive impairment (developmental disorders, mental retardation)	44	17
Anxiety disorders (anxiety, post-traumatic stress disorder)	17	6
Mood/affective disorders (bipolar disorder, mania, depression)	13	5
Psychotic disorders (schizophrenia, delusional disorders)	12	5
Tic disorders	12	5
Other diagnosis (epilepsy, self-harm)	8	3
No specific diagnosis	15	6

a Of 250 children with a specific diagnosis, 180 had one diagnosis reported and 70 children had two diagnoses. Of these, 12 children had two diagnoses in the same diagnostic group and have not been counted twice.

b Proportion of the 265 children who had a diagnosis/indication for use identified.

ADHD = attention deficit and hyperactivity disorder.

four were spontaneous reports. In total, 352 clinical adverse events were identified, of which 331 (229 incidents and 102 reactions) occurred in patients taking risperidone. In patients prescribed quetiapine, there were 15 events (12 incidents and 3 reactions).

Most Frequent Adverse Events in Risperidone Recipients

The most frequent adverse events in children taking risperidone are shown in table IV. Weight increase, dental caries, dental extractions and somnolence were the most commonly identified adverse events in these children.

Dystonic Reactions

The six dystonic reactions identified in risperidone recipients included three patients with torticollis, one child with neck and facial dystonia, one child with back cramps 5 days after starting risperidone (the reporting doctor specified this as a dystonic reaction) and one patient admitted to hospital with torsion dystonia. In addition to these reports, there was an interesting report of palpebral ptosis in a 5-year-old girl prescribed risperidone 4 mg/day. The ptosis in this child resolved upon dose reduction and the reporting doctor considered it to be related to risperidone treatment. There was also a report of

Table III. Target symptoms in children aged ≤15 years who were treated with atypical antipsychotics

Target symptom	Total[a]	Proportion (%)[b]
Aggression (rages, tantrums, anger, explosive behaviour, violent behaviour)	97	47
Behavioural difficulties (difficult, unmanageable, disruptive, oppositional, defiant)	54	26
Anxiety (agitation, irritability, excitement)	36	17
Hyperactivity (attention deficit, impulsivity)	20	10
Mood disturbances (mood fluctuations/instability, emotional outbursts, mania, depression)	19	9
Psychotic symptoms (visual and auditory hallucinations, delusions)	15	7
Obsessive/compulsive symptoms	5	2
Self-harming behaviour	8	4
Sleep disturbances (insomnia, poor sleep, nightmares, sedation)	7	3
Tics/movement disorders	8	4
Other symptoms (autistic symptoms, social inappropriateness, tangential thinking, sensory overload, negativism, articulation)	13	6

a 134 patients had one target symptom reported and 74 patients had two target symptoms reported.

b Proportion of the 208 children for whom the target symptom was identified.

Table IV. Incidence of the ten most frequent adverse events[a] in children aged ≤15 years who were taking risperidone

Adverse event	Number of events	Incidence (total cohort; n = 391)		Incidence (population for whom a follow-up questionnaire was completed; n = 271)	
		cumulative %	per 100 patient-years	cumulative %	per 100 patient-years
Weight increase	29	7.4	4.8	10.7	5.9
Dental caries	22	5.6	3.6	NA[b]	NA[b]
Dental extraction	18	4.6	2.9	NA[b]	NA[b]
Somnolence[c]	11	2.8	1.8	4.0	2.3
Otitis media	10	2.6	1.7	3.7	2.1
Appetite increased	8	2.0	1.3	3.0	1.6
URTI	8	2.0	1.3	3.0	1.6
LRTI	7	1.8	1.2	2.6	1.4
Other infections[d]	14	3.6	2.3	5.2	2.9
Dystonic reactions[e]	6	1.5	1.0	2.2	1.2

a Includes events obtained from both the follow-up questionnaire and those identified using record linkage for each of the cohorts analysed.

b None of these events were identified from follow-up questionnaires.

c The events 'tiredness' and 'fatigue' have been included in this term.

d Includes skin infection (2), dental abscess (1), infectious diarrhoea (2), herpes infection (2), chicken pox (1), threadworms (1), influenza (2), viral infection (2) and infection unspecified (1).

e Includes torticollis/neck stiffness (3), dystonic reaction of face and neck (1), dystonic reaction involving back cramps (1) and torsion dystonia (1).

LRTI = lower respiratory tract infection; **NA** = not applicable; **URTI** = acute respiratory tract infection.

blepharospasm and facial grimacing in a 13-year-old boy taking risperidone 1 mg/day to treat sleeping difficulties and aggression. It was specified that there were no signs of tardive dyskinesia in this patient.

Diabetes Mellitus

In the study population prescribed risperidone for whom we received a returned questionnaire (n = 271 children), we identified two reports of diabetes mellitus. A 13-year-old boy developed new-onset diabetes 27 months after starting risperidone treatment and another 9-year-old boy experienced worsening of pre-existing diabetes resulting in severe diabetic ketoacidosis and encephalopathy. The estimated incidence of new-onset diabetes/worsening diabetes in this population, who represented 489 patient-years of treatment, was 4 (95% CI 0.5, 15) cases per 1000 patient-years. Two other children were reported to have developed polyuria (one also had polydipsia) whilst taking risperidone, but neither was confirmed as developing diabetes during the follow-up period.

Depression

Events were only coded as 'depression' by IMMP medical assessors if the reporting doctor specified these symptoms in their report. Using these criteria, four children were identified as having developed symptoms of depression whilst taking risperidone. The brief details of these cases are as follows:

1. The mother of a 13-year-old girl with autism noted that her daughter became 'sad and emotionally blunted' after starting treatment with risperidone. Risperidone treatment was stopped with resolution of these symptoms. Concomitant medicines received by this child included methylphenidate, amitryptyline (10 mg/day administered at night) and clonidine.
2. A child psychiatrist reported that an 11-year-old boy with Asperger's syndrome became significantly depressed 11 months after starting risperidone treatment and it was stopped for this reason. Quetiapine treatment was initiated after risperidone was withdrawn.
3. A 10-year-old boy with Oppositional Defiant Disorder became tearful and tired in the mornings 3 months after starting risperidone treatment. This patient was not receiving any concomitant medications. His psychiatrist related the symptoms of depression to risperidone treatment and reduced the dosage. Attempts to reduce the dose were unsuccessful because the patient's behaviour deteriorated rapidly.
4. A 15-year-old boy was prescribed risperidone 0.5–1 mg/day for conduct disorder and attention deficit and hyperactivity disorder. This patient was not receiving any concomitant medications. About 16 months after starting risperidone treatment, he developed depressed mood associated with an adjustment disorder and cut his wrists. Risperidone treatment was continued and the depressive episode resolved.

These four cases gave an incidence of depression in the population for whom follow-up questionnaires were returned (489 patient-years of exposure) of 8 (95% CI 2.0, 21) cases per 1000 patient-years of treatment.

Other possible cases of depression that were reviewed included an 11-year-old boy with Asperger's syndrome (who was receiving risperidone for aggressive behaviour) who developed suicidal thoughts and refused to go to school, but the doctor did not specify that the child was clinically depressed. There was also one report of intentional overdose and five further reports of intentional self-harm, but on further assessment (and follow-up enquiry where indicated) none of these was considered to be related to the antipsychotic medication. These seven cases were therefore not coded as events of depression.

Other Adverse Reactions

There were other reports of known adverse reactions to atypical antipsychotic medicines including nocturnal enuresis (3 reports), hyperprolactinaemia (2), constipation (5), epistaxis (1) elevated blood pressure (1) and hypertriglyceridaemia (1).

Reasons for Cessation of Therapy

Of 275 valid questionnaires returned, 73 patients (26.5%) were reported to have stopped the atypical antipsychotic prescribed during this study. Table V

Table V. Reasons for cessation in the 73 children aged ≤15 years who discontinued atypical antipsychotic therapy

Reason	Number of patients for which this reason was reported	Proportion of cohort[a] (%) [n = 275]	Proportion reasons for cessation (%)
No longer needed	31	11	35
Adverse reaction	21	8	24
Inadequate therapeutic response	18	7	20
Poor compliance	6	2	7
Other reason unrelated to medicine	7	3	8
Patient died	2	1	2
Reason not stated	3	1	4
Totals	**88**	**32**	**100**

a Population for whom an assessable questionnaire was returned.

shows the reported reasons for stopping the medicine.

Discussion

This post-marketing study provides a 'real-life' picture of the safety and usage of atypical antipsychotics in a nationwide cohort of children. Compared with most previous reports of the use of these medicines in children,[3] our study included a larger number of patients, had no exclusion or inclusion criteria, longer durations of treatment, longer periods of follow-up and was independent of the pharmaceutical industry. Another advantage of a national cohort study is that the results may be more generally representative compared with studies performed in selected populations – for example, studies in insured patients.[2,10]

Most children in this cohort were prescribed risperidone. This is consistent with risperidone having the largest published paediatric evidence base[3] and being the only atypical antipsychotic licensed for use in children.[11] The mean observed duration of treatment of approximately 18 months reflects the practice of long-term use of these medications in many children.

The most common diagnoses in our population were disruptive disorders. This is consistent with studies supporting the effectiveness of risperidone in these conditions,[12-15] and with the findings of a recent study of American youths in a public mental health system.[16] However, some reported reasons for use, including anxiety and pervasive developmental disorders, were outside the terms of the NZ product licences in 2003.

The collection of data on target symptoms is a unique feature of our study - this has not previously been investigated in other studies. The most frequently reported target symptoms (aggression and difficult behaviour) were consistent with the most common diagnoses reported. However, an unexpected finding was the use of atypical antipsychotics to treat sleep disorders. Five of the seven children for whom sleep disorder was specified as a target symptom had other target symptoms specified, but two children did not. The use of atypical antipsychotics for nocturnal sedation of children may be of some concern and is outside the product licence indications.

About 30% of the children in this study were identified as having experienced an adverse event, with about one-third of these events considered to be causally related to the antipsychotic medicine. This illustrates the intensive PEM methodology used, which identifies all new clinical adverse events, some of which are unrelated 'incidents' or background noise.[6] This methodology is effective for identifying new signals from events initially assessed as incidents.[17]

The finding of reported weight gain in 11% of children is consistent with studies that have examined this more closely;[12,18] however, it is likely to be an underestimate due to the observational methodology of our study. Another study reported weight gain in 36% of children taking risperidone[19] and

this is now a recognised adverse effect of these drugs.[20]

Somnolence/sedation is also commonly reported in children receiving risperidone, with a frequency of around 30% in several studies.[12-14] Our study identified somnolence in only 4% of risperidone recipients. This lower incidence may reflect underreporting due to the 'open question' design of IMMP questionnaires compared with the direct questioning of patients in most clinical trials. However, it may also suggest that in real-life use of risperidone, somnolence is a less significant issue.

The finding that approximately 6% of the cohort had hospital admissions for dental caries was unexpected. This incidence is higher than the estimated 'background' in New Zealand, where annual hospitalisations for dental caries occur in <1% of children aged ≤15 years.[21] Whilst our study has identified this issue, any causal relationship of dental caries with atypical antipsychotics could not be fully evaluated. Further study is required to investigate all the factors that might be responsible for hospital admissions for dental caries in these children.[22]

It is recognised that atypical antipsychotics may precipitate hyperglycaemia and diabetes, but information regarding this adverse effect in children is limited to case reports[23] and analyses of spontaneously reported adverse events.[24] We could not find any published studies that had been able to calculate the incidence of new-onset diabetes (or worsening of diabetes) in a paediatric population who had been prescribed atypical antipsychotics. Thus, the estimated incidence of 4 cases per 1000 patient-treatment years from our study is useful, although with the small number of cases the confidence intervals were wide. A larger study population would be needed to study this important issue further. Data from the US suggest that less than one incident case of diabetes per 1000 persons occurs yearly for the population aged 0–24 years;[25] therefore, the incidence may be increased in children prescribed atypical antipsychotic medications.

In this study, we identified four cases of depression that were causally related to risperidone, giving an estimated incidence of 8 cases per 1000 patient-years of treatment. This may be an underestimate as other cases of suicidality/self-harm were identified; however, depression was only recorded as an event if doctors specifically reported these symptoms or if we could confirm that the child had developed symptoms of depression.

Risperidone has not previously been associated with depression in children, although in a study of 48 children followed for 2 years, one child discontinued risperidone treatment because of symptoms of depression.[15] A retrospective study of 58 adult and adolescent patients with Gilles de la Tourette's syndrome who received risperidone found that 17 (29%) developed major depressive disorder, including one patient who later committed suicide.[26] However, depression is common in patients with Gilles de la Tourette's syndrome[27] and, therefore, this study could not determine if causality was related to the disease or the drug.

In our study, symptoms of depression developed in children without previous mood disorders, who were being treated for indications not usually associated with depression. Risperidone has recognised effects on mood, having high affinity for serotonergic $5HT_2$ receptors, and is licensed for the treatment of mania in adults.[11] We therefore believe that depressive symptoms represent a new signal (i.e. a previously unidentified adverse reaction) for risperidone in children. However, depression is difficult to investigate due to confounding factors in children treated with atypical antipsychotics. Treatment of disruptive behaviour or other problems may also unmask underlying depression that was not previously evident. Although the association of risperidone with depression in children needs further study, we would advise clinicians to be aware of the possible emergence of these symptoms, especially because of the potentially serious consequences.

Conclusion

We believe this nationwide study of the 'real-life' use of atypical antipsychotic medicines in children has provided useful data on both usage and safety. The reasons for use of these medications in

children largely appear to reflect clinical practice and are consistent with other studies. Most prescriptions were for risperidone and the most common diagnoses being treated were disruptive disorders. The detailed information obtained on target symptoms is clinically relevant, with the observation of use of these medicines to sedate some children being of some concern. Regarding safety, approximately one-third of our cohort experienced an adverse clinical event during this study, although not all events were considered to be causally related to the atypical antipsychotic medicine. Many of the known safety issues with these drugs (e.g. weight gain, dystonic reactions) have been confirmed in this population. The most significant finding was that symptoms of depression may develop in children receiving risperidone. Whilst further investigation of this issue is now needed, we advise clinicians and other carers of these children to be aware of this possible new signal.

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Dr Mira Harrison-Woolrych conceived and designed this study, supervised the conduct of the study, is responsible for the raw data collected, supervised and checked the clinical assessments performed, designed and conducted the analyses, interpreted the findings (with the other authors) and wrote the manuscript.

Dr Juan Garcia-Quiroga advised on the design of this study, in particular the clinical aspects of the follow-up questionnaire. He has been involved with the study from its inception and helped with liaison with child and adolescent psychiatrists throughout New Zealand. He also helped perform literature searches, has reviewed all drafts of the manuscript and approved the final version.

Mrs Janelle Ashton was responsible for all data extraction from the IMMP databases for this study, performed the required analyses and contributed to interpretation of the data. She has also reviewed all drafts of the manuscript and approved the final version.

Associate Professor Peter Herbison provided biostatistical advice on the design of this study and the analyses performed. He has also reviewed the manuscripts and approved the final version.

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