SHORT COMMUNICATION

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Paediatric Atypical Antipsychotic Monitoring Safety (PAMS) Study

Pilot Study in Children and Adolescents in Secondary- and Tertiary-Care Settings

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Abstract

Background: In the UK, treatment with antipsychotic medications for children is usually initiated by specialists in secondary care. Recent studies have shown an increase in the prescribing of atypical antipsychotics in children. The severity of possible adverse effects to antipsychotics in adults has lead to awareness of the importance of investigating the potential adverse effects of these agents in children. Additionally, there have been many reports proposing that the newer atypical antipsychotics are associated with many of the same adverse effects seen with the older generation drugs in children. The aim of the Paediatric Atypical Antipsychotic Monitoring Safety (PAMS) study was to determine the feasibility of conducting a prospective targeted pharmacovigilance study to monitor adverse drug reactions (ADRs) associated with atypical antipsychotic therapy in children seen in secondary- and tertiary-care settings.

Methods: Participants were identified from the clinical members of the UK Paediatric Psychopharmacology Groups in London and the West Midlands. Participating clinicians reported the number of patients (aged ≤18 years) taking atypical antipsychotic treatment who were under their care and any reportable ADRs experienced by these patients during the period September 2006–September 2007. Participants contributed data via password protected online data collection forms.

Results: A total of 35 clinicians consented to participate in the study. However, data from 22 of the participating clinicians were excluded because of incomplete reporting. Data from the remaining 13 (37%) clinicians were eligible for the final analysis. There were 281 patients who received atypical antipsychotic treatment under the care of the 13 participating clinicians.

From these 281 patients, 40 ADR reports (0.14 ADR reports per patient; 95% CI 0.10, 0.19) from 37 patients were entered into the database. Of the 37 patients, 13 experienced more than one ADR, bringing the total number of ADRs to 56 (0.20 ADR per patient; 95% CI 0.15, 0.25). The most commonly reported ADRs were weight gain, extrapyramidal symptoms and hyperprolactinaemia. Rare ADRs, including neuroleptic malignant syndrome, were also reported. The durations of atypical antipsychotic drug exposure were recorded for 54 of the 56 ADRs reported. The median duration of exposure was 42 days (interquartile range 23.25–90 days).

Conclusions: Our study demonstrates that a clinician-based targeted pharmacovigilance study on atypical antipsychotics in children provides useful qualitative data. However, this pilot study raised many methodological issues, which should be addressed for the study to be extended nationally. Specifically, significant funding is needed to improve the reporting rate and the overall data obtained. Furthermore, the study yielded a very high incidence of serious ADRs, thus supporting the need for a larger and improved pharmacovigilance study to evaluate the safety of atypical antipsychotics in children.

Background

In the UK, treatment with antipsychotic medications for children is usually initiated by specialists in secondary care such as child psychiatrists and consultant paediatricians.[1] Studies in children and adolescents have shown that antipsychotic agents are effective in the treatment of psychiatric disorders including pervasive developmental disorders, disruptive behavioural disorders, aggression and tic disorders.[2,3] The second-generation antipsychotics, atypical antipsychotics, were first introduced in the late 1980s and are considered to have some advantages over the older typical antipsychotics, such as a reduced incidence of movement disorders.[4-6]

Since their introduction, the use of atypical antipsychotics has been increasing and has largely replaced the older typical antipsychotics in children and adolescents.[7,8] However, despite the evident increase in use, the safety profile of these agents in this population has not yet been fully established. The severity of possible adverse effects of antipsychotics in adults has lead to awareness of the importance of investigating the potential adverse effects of these agents in children and adolescents.[9] In general, it is unwise to extrapolate safety data from studies in adults to children as there are significant variations due to age and development in both drug pharmacokinetics and pharmacodynamics. Furthermore, the long-term effects of early treatment with psychotropic drugs have also not been fully studied.[10] Although cases of serious adverse drug reactions (ADRs) such as neuroleptic malignant syndrome[11] and liver damage[12] have been reported, there have been few well designed clinical studies in children to systematically evaluate ADRs associated with atypical antipsychotic use in this target population.

In the past, the safety of medicines was mainly monitored by spontaneous reporting schemes. However, under-reporting is a recognized problem with this method; particularly with off-label and unlicensed use of medicines in children. Due to this reason, a Royal College of Paediatric and Child Health (RCPCH) report recommended the use of targeted pharmacovigilance to monitor drug safety in children.[13] Targeted pharmacovigilance is focused on monitoring the safety profiles of specific groups of drugs in relation to specific ADRs. This method has led

to the development of evidence-based guidelines to reduce drug toxicity regarding particular groups of drugs.[13,14] Therefore, targeted pharmacovigilance should be essential when investigating the safety of atypical antipsychotics in the young.

The aim of the Paediatric Atypical Antipsychotic Monitoring Safety (PAMS) Study was to determine the feasibility of conducting a prospective targeted pharmacovigilance study to monitor ADRs associated with atypical antipsychotic treatment in children and adolescents.

Methods

Setting

The setting for this study was secondary and tertiary paediatric/adolescent mental health inpatient and outpatient units.

Participants

Participants were identified from the UK Paediatric Psychopharmacology Groups (PPGs) in London and the West Midlands. The members of the PPGs include consultant paediatricians, consultant child and adolescent psychiatrists, and paediatric pharmacists. Inclusion criteria were clinical practitioners within the PPG who initiated new treatments with atypical antipsychotic medication for children and adolescents (defined as patients aged ≤18 years). Exclusion criteria were clinicians who did not prescribe atypical antipsychotics regularly (i.e. at least one prescription every 2 months).

Reporting Criteria

The participants reported the number of patients taking atypical antipsychotics who were under their care. This included the baseline number of patients when the study began, and the number of patients starting and the number of patients stopping atypical antipsychotic treatment throughout the duration of the study.

Secondly, the participants reported all children and adolescents who fulfilled the inclusion criteria specified above who developed reportable ADRs. An ADR was considered reportable if it (i) required termination of treatment of the atypical antipsychotic and/or a required treatment of the suspected ADR; (ii) was an ADR previously unknown, in the reporting clinician's opinion; or (iii) was considered 'serious' as defined in the International Conference on Harmonization Guideline for Clinical Safety Data Management[15] (i.e. any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect).

When reporting an ADR, participants were asked to provide patient demographic details including gender, as well as month and year of birth; atypical antipsychotic details including name of antipsychotic, dose and duration of treatment as well as indications; ADR details including symptoms and outcome of the ADR being reported, and actions required in the management of the ADR; and additional details including concurrent medication and any other additional information related to the ADR being reported.

Confidence intervals for the rate of ADRs reported by type of drug were calculated using Stata SE 9.1 (Stata Corp, College Station, TX, USA).

Data Collection

Participants contributed data via a password protected online data collection form. Data collection was from September 2005 to September 2006. Ethical approval was granted by a UK Multicentre Research Ethics Committee.

Results

Approximately 100 clinicians from the London and West Midlands PPGs were approached to participate in the study. From these, a total of 35 clinicians consented to participate. Data from 22 of the participating clinicians were excluded because of incomplete reporting. Data from the remaining 13 (37%) participating clinicians were eligible for the final analysis.

There were a total of 281 patients who were taking atypical antipsychotic treatment under the

care of the 13 participating clinicians. From these 281 patients, there were 40 ADR reports (0.14 reports per patient; 95% CI 0.10, 0.19) from 37 patients. Of the 37 patients, 13 experienced more than one ADR, bringing the total number of ADRs to 56 (0.20 ADR per patient; 95% CI 0.15, 0.25). The median age of patients who experienced ADRs was 15 years (interquartile range 10–17 years).

Although the highest number of reports was related to risperidone use, risperidone was also the most common atypical antipsychotic prescribed and in fact had the lowest rate of ADRs. Because of the relatively small sample size, the rates of ADRs by type of atypical antipsychotic demonstrate wide confidence intervals, as shown in table I. The most common atypical antipsychotic prescribed was risperidone (55.7% of patients), followed by aripiprazole (20.0%), olanzapine (11.1%), quetiapine (5.7%), clozapine (2.9%) and amisulpride (2.5%). The most reported ADRs according to drug correlated with the number of patients on treatment for risperidone, aripiprazole, olanzapine and amisulpride. The number and types of ADRs reported were grouped into seven different categories (table I). Durations of atypical antipsychotic drug exposure were recorded for 54 of the 56 ADRs reported. The median duration of exposure was 42 days (interquartile range 23.25–90 days).

Discussion

There has been substantial public interest about the safety of drug use in children. This interest, coupled with concern over the potential effects of psychotropic medications on physical and brain development, means that it is important to identify and develop valid methods for detecting possible drug-induced adverse effects associated with drug exposure.[16] To our knowledge, this is the first targeted pharmacovigilance study to monitor ADRs associated with atypical antipsychotic medication in children and adolescents in the UK secondary and tertiary settings. The results of this pilot study raise many key methodological issues related to conducting such a study nationally.

Methodology of the PAMS Study

Currently available methodologies related to pharmacovigilance are ill-equipped to deal with long-term ADRs in children, not only atypical antipsychotic therapy but almost all drugs. The only possible resources are electronic patient records, which could link up all drug treatments and clinical outcomes from primary, secondary and tertiary care; however, such a system is not yet available. Hence, the European Medicines Agency have called for more research with specific methodologies and investigations into the long-term safety of paediatric medicines, specifically off-label medicines.[17,18]

By using clinicians as the study data source, we managed to obtain in-depth data in relation to the ADRs reported. The reports provided useful qualitative data such as patient demographics, dose and duration of drug exposure, ADR symptoms, management and outcomes, and other important details such as concurrent medication. Furthermore, as the participating clinicians were volunteers, the study cost was minimized.

Additionally, a sample of patients and ADRs from one tertiary practice was independently reviewed and assessed by an investigator (FAR). It was found that the data included by this practice was of high quality and all the ADRs reported were confirmed. Therefore, this pilot study has demonstrated that the evaluation and validation of data is possible.

However, because the study was clinician-based, the majority of participants were subject to time constraints, which limited the amount of data contributed, specifically data on the number of patients exposed to treatment. Without this, analysis on the rate of ADRs was limited because of an absence of accurate information on the clinic populations, including the true frequency of prescriptions to provide a denominator.

Moreover, the level of data required for this study called for a high amount of commitment from the participating clinicians. As the participants were a volunteer force, there were no specific incentives for them to contribute to the study. This might have lead to skewed results

Table I. Number of adverse drug reactions (ADRs) reported by category

Category	Number of ADRs						
	risperidone	aripiprazole	olanzapine	clozapine	quetiapine	amisulpride	total
Category 1: general disorders							
Flu-like symptoms		1					1
Encopresis	1						1
Raised creatinine kinase levels	1						1
Fever		1		1			2
Neuroleptic malignant syndrome			1				1
Total	*2*	*2*	*1*	*1*			*6*
Category 2: endocrine and metabolism disorders							
Raised triglycerides				1			1
Hyperprolactinaemia	3	1				3	7
Weight gain	11	1	2		3		17
Total	*14*	*2*	*2*	*1*	*3*	*3*	*25*
Category 3: psychiatric disorders							
Behaviour disorders		1			1		2
Total		*1*			*1*		*2*
Category 4: nervous system disorders							
Headaches		1					1
Sedation			1				1
Extrapyramidal symptoms	2	4	2			1	9
Total	*2*	*5*	*3*			*1*	*11*
Category 5: cardiac, blood and vascular disorders							
Tachycardia	2			1			3
Hypotension			1	1	1		3
Neutropenia				2			2
Total	*2*		*1*	*4*	*1*		*8*
Category 6: gastrointestinal disorders							
Abdominal pains	1						1
Nausea	1						1
Total	*2*						*2*
Category 7: renal and urinary disorders							
Enuresis	1	1					2
Total	*1*	*1*					*2*
Overall total	**23**	**11**	**7**	**6**	**5**	**4**	**56**
Number of patients receiving treatment	**156**	**56**	**38**	**8**	**16**	**7**	**281**
Rate of ADR (95% CI)	**0.15 (0.09, 0.21)**	**0.20 (0.10, 0.32)**	**0.18 (0.08, 0.34)**	**0.75 (0.35, 0.97)**	**0.31 (0.11, 0.59)**	**0.57 (0.18, 0.90)**	**0.20 (0.15, 0.25)**

where only the more committed participants were the source of data. Conceivably, these clinicians may represent the most enthusiastic practitioners who were more likely to prescribe for novel indications or at British National Formulary limits rather than the 'average' clinician. The final analysis would then not portray the 'real life scenario' of typical psychopharmacotherapy practitioners.

We are currently considering extending the PAMS study nationally and therefore certain methodological issues are to be addressed. The participants for this pilot study were given initial training in the way of brief instruction during

PPG meetings and electronically via e-mail. A comprehensive training programme for future participants by means of one-to-one training may help improve the reporting rate of participating clinicians, specifically the reporting of the number of patients receiving treatment. As well as training, the implementation of clearer definitions of ADRs, the need to report and whether treatment was stopped as a result of the ADR(s) should be decided upon in future studies. Although relatively strict criteria was implemented for ADR reporting in this study, it was ultimately at the participating clinician's discretion on whether to report or not. While clear definitions might assist clinicians on reporting ADRs in future studies, the availability of strict criteria might inhibit the overall reporting of ADRs. Therefore, this matter should be agreed upon using a consensus panel consisting of paediatric psychopharmacologists and experienced researchers.

With the appropriate funding, incentive payments can also be provided for participating clinicians who contribute data. An example would be the Child and Adolescent Psychiatry Trials Network (CAPTN), which currently has over 200 practicing child and adolescent psychiatrists in the US and Canada.[19] CAPTN sets up contracts for clinicians upon participation and provides incentives that include research costs at an hourly rate. This network provides the opportunity for members to interact and share knowledge, participate in and contribute to various research projects, and ultimately improve the care of paediatric patients. Alternatively, a wider reporting scheme such as that used by the British Paediatric Surveillance Unit (BPSU), which is funded by the Department of Health, may be considered. The BPSU enables paediatricians to participate in the surveillance and study of rare disorders affecting children. A constraint to this method is the lack of accurate baseline data. Our study allowed for data on a number of patients receiving treatment to be collected, which can then be used to calculate a proxy of ADR incidence from the proportion of ADRs to the number of new starters per month and involved both child psychiatrists as well as paediatricians as data sources. Consequently, data obtained from a future study design complementing the current BPSU surveillance project will be particularly valuable as a BPSU or psychiatry surveillance system of atypical antipsychotics in children has yet to be set up.

The majority of participating clinicians also found it difficult to report the number of patients (including baseline and follow-up number of patients) on treatment, which in turn limited the analysis of rate of ADRs reported. This can be overcome in the future by limiting the study to new patients where participants only report the number of patients newly starting atypical antipsychotic treatment. However, this might actually limit the number of patients included in future studies. In this pilot study, clinicians who had pre-existing patients on atypical antipsychotic agents were also included and the baseline number of patients from each participating clinician was analysed in the results. These clinicians were also expected to initiate new treatment so that acute ADRs could be monitored after the initiation of treatment.

While as many clinicians as possible should be included in the analysis of this pilot study, there was the question of labour and logistics. When conducting clinical studies in the UK, Research and Development approvals from local National Health Service (NHS) Trusts are required in addition to ethics committee approval. This process may take several months (up to 8 months for this pilot study) and was considered not cost effective. Therefore, in this pilot stage, it was considered to be unfeasible to include clinicians who prescribed atypical antipsychotic agents infrequently.

Additionally, during a post-mortem meeting, where the study results and methodology were discussed with members of the London PPG, it was the general consensus of the group's clinical members that research assistants would greatly improve the reporting rate and quality of data contributed by future participants. Consequently, with the appropriate funding, research assistants could be employed to collect information on the number of patients on treatment (both pre-existing patients and patients newly starting atypical antipsychotic therapy) from different practices. This would also reduce the possibility

of duplicate reporting, especially in practices with more than one participating clinician.

Furthermore, the database resulting from the future study could also be accessed by participating clinicians. This would offer a detailed, organized method of storing relevant clinical information concerning patients under their care, including therapy details, ADRs and treatment outcomes. This may then help improve clinical practice for participating clinicians.

In summary, the availability of PPGs around the UK provides a potentially useful research network that is currently under-used. Research networks consisting of practicing clinicians could potentially provide a wide range of benefits, from providing data for efficacy and safety research, as well as an available network for interaction and sharing of specialist knowledge. In addition, the involvement of experienced, prominent clinicians within the PPGs provides expert input into prospective future studies. A surveillance, or targeted pharmacovigilance system conducted in such a practice-based network would also allow for a large sample of study subjects and good representation of real-world clinical paediatric patients.

Adverse Drug Reactions Reported

Despite the relatively small number of patients under the care of the participants, the study managed to capture uncommon and rare ADRs such as enuresis and neuroleptic malignant syndrome (NMS). NMS is considered a very rare event in adults (for example the incidence is estimated to be <0.01% with olanzapine[20]) and is a potentially fatal adverse effect associated with the use of antipsychotic medications. To our knowledge, the rate of this event in children exposed to olanzapine is not known.

The earliest case of NMS can probably be traced back to 1959, which occurred in a patient exposed to trifluoperazine, a typical antipsychotic agent.[21] Practically all antipsychotic drugs are capable of producing NMS.[22] The clinical manifestations of NMS include high fever, muscle rigidity and elevated creatine phosphokinase.[11,22-24]

The rate of ADRs reported was also extremely high, with one in every five patients experiencing an ADR. Again, this may be because the data were reports from more enthusiastic or committed participating clinicians who were vigilant in detecting and reporting ADRs. Nevertheless, we cannot exclude the possibility of a high rate of ADRs in children who are treated with atypical antipsychotics.

The most commonly reported ADRs were related to endocrine and metabolism disorders, and the single most reported ADR was weight gain. In the young, weight gain may have a particularly detrimental effect as it predicts an increased morbidity and mortality associated with obesity, cardiovascular disease and metabolic syndrome in adulthood.[25,26] As atypical antipsychotic prescribing has been shown to be increasing in the paediatric population,[7] further investigations on the potential significance of weight gain as well as appropriate monitoring and treatment in children exposed to these agents should be prioritized.

The potential adverse effects of atypical antipsychotic agents are thought to be comparatively similar due to the similar pharmacological action.[27] This presents a prescribing problem to practitioners treating patients with neuropsychiatric conditions from this population as the choice of medications available for children and adolescents is relatively limited. As most of these drugs are used outside their licensed indications in patients aged <18 years, there is also a lack of dosing guidelines available for clinicians. Furthermore, although we have demonstrated good qualitative data, there was not enough power to compare the rate of ADRs by different type of drug because of the relatively small sample size of our study. This also resulted in wide confidence intervals of ADR rates. Consequently, it is essential to design and conduct better pharmacovigilance studies to evaluate the safety of atypical antipsychotics in this target population.

Conclusions

Our study demonstrated that a clinician-based targeted pharmacovigilance study of atypical antipsychotics in children provides useful qualitative

data. For future studies we recommend that more exacting research designs will be needed to ensure rigorous and accurate data collection. Specifically research funding is required to recruit and support pharmacovigilance in a wider sample of NHS clinics where children are treated with antipsychotics by providing for the costs of supervision and high quality on-site data collection. Furthermore, the study yielded a very high rate of ADRs, indicating an urgent need for improved pharmacovigilance studies to evaluate the safety of atypical antipsychotics in children.

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References

1. Bramble D. Annotation: the use of psychotropic medications in children: a British view. J Child Psychol Psychiatry 2003; 44 (2): 169-79
2. Anderson L, Campbell M, Grega D, et al. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry 1984; 141 (10): 1195-202
3. Naruse H, Nagahata M, Nakane Y, et al. A multi-center double-blind trial of pimozide (Orap), haloperidol and placebo in children with behavioral disorders, using crossover design. Acta Paedopsychiatry 1982; 48: 173-84
4. Frangou S, Byrne P. How to manage the first episode of schizophrenia. BMJ 2000; 321: 522-3
5. Malone R, Sheikh R, Zito J. Novel antipsychotic medications in the treatment of children and adolescents. Psychiatr Serv 1999; 50 (2): 171-4
6. Cheng-Shannon J, McGough J, Pataki C, et al. Second-generation antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol 2004; 14 (3): 372-94
7. Rani F, Murray ML, Byrne PB, et al. Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. Pediatrics 2008; 121 (5): 1002-9
8. Martin A, Leslie D. Trends in psychotropic medication costs for children and adolescents, 1997-2000. Arch Pediatr Adolesc Med 2003; 157 (10): 997-1004
9. Laita P, Cifuentes A, Doll A, et al. Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. J Child Adolesc Psychopharmacol 2007; 17 (4): 487-501
10. Vitiello B, Riddle MA, Greenhill LL, et al. How can we improve the assessment of safety in child and adolescent psychopharmacology? J Am Acad Child Adolesc Psychiatry 2003; 42 (6): 634-41
11. Hanft A, Eggleston CF, Bourgeois JA. Neuroleptic malignant syndrome in an adolescent after brief exposure to olanzapine. J Child Adolesc Psychopharmacol 2004; 14 (3): 481-7
12. Kumra S, Herion D, Jacobsen LK, et al. Case study: Risperidone induced hepatotoxicity in pediatric patients. J Am Acad Child Adolesc Psychiatry 1997; 36 (5): 701-5
13. Royal College of Paediatrics and Child Health. Safer and better medicines for children: developing the clinical and research base of paediatric pharmacology in the United Kingdom. A review commissioned by the Medical Research Council, the Department of Health, and the Association of British Pharmaceutical Industry. May 2004 [online]. Available from URL: http://www.rcpch.ac.uk/Publications/Publications-list-by-date [Accessed 2008 Feb 7]
14. Choonara I. Paediatric pharmacovigilance. Paediatr Perinat Drug Ther 2006; 7 (2): 50-3
15. ICH harmonised tripartite guideline. Clinical safety data management: definitions and standards for expedited reporting 1994 [online]. Available from URL: http://www.ich.org/LOB/media/MEDIA436.pdf [Accessed 2008 Jan 3]
16. Greenhill LL, Vitiello B, Abikoff H, et al. Developing methodologies for monitoring long-term safety of psychotropic medications in children: report on the NIMH conference, September 25, 2000. J Am Acad Child Adolesc Psychiatry 2003; 42 (6): 651-5
17. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on conduct of pharmacovigilance for medicines used by the paediatric population: post-authorisation evaluation of medicines for human use. Jan 2007 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/phvwp/23591005en.pdf [Accessed 2008 Dec 17]
18. European Medicines Agency. Revised priority list for studies into off-patent paediatric medicinal products: pre-authorisation evaluation of medicines for human use. Aug 2008 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/paediatrics/22698308en.pdf [Accessed 2008 Sep 29]
19. Child and Adolescent Psychiatry Trials Network [online]. Available from URL: http://www.captn.org [Accessed 2008 Jan 22]
20. Electronic medicines compendium. Zyprexa 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg coated tablets. Zyprexa Velotab 5 mg, 10 mg, 15 mg, and 20 mg orodispersible tablets [online]. Available from URL: http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=614 [Accessed 2008 Feb 6]
21. Brown TM. Clozapine, neuroleptic malignant syndrome, and pancerebellar syndrome. Psychosomatics 1999; 40 (6): 518-20

22. Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malignant syndrome: a review. Psychiatr Serv 1998; 49 (9): 1163-72
23. Levenson J. Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142 (10): 1137-45
24. Gracious BL, Findling RL. Antipsychotic medications for children and adolescents. Pediatr Ann 2001; 30 (3): 138-45
25. Correll CU. Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. J Am Acad Child Adolesc Psychiatry 2007; 46 (6): 267-700
26. Stigler KA, Potenza MN, Posey DJ, et al. Weight gain associated with atypical antipsychotic use in children and adolescents. Pediatr Drugs 2004; 6 (1): 33-44
27. Burns MJ. The pharmacology and toxicology of atypical antipsychotic agents. Clin Toxicol 2001; 39 (1): 1-14

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