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SYSTEMATIC REVIEW

The Safety of Olanzapine in Young Children: A Systematic Review and Meta-Analysis

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Abstract

Background Olanzapine is frequently prescribed in young children for psychiatric conditions. It may be an option for chemotherapy-induced nausea and vomiting (CINV) control in children. The objective of this review was to describe the safety of olanzapine in children less than 13 years of age to determine if safety concerns would be a barrier to its use for CINV prevention.

Methods Electronic searches were performed in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science and Scopus. All studies in English reporting adverse effects associated with olanzapine use in children younger than 13 years or with a mean/median age less than 13 years were included. Adverse outcomes were synthesized for prospective studies.

Results A total of 47 studies (17 prospective) involving 387 children aged 0.6–18 years were included; nine described olanzapine poisonings. Weight gain or sedation were reported in 78 % [95 % confidence interval (CI) 63–95] and 48 % (95 % CI 35–67), respectively. Extrapyramidal symptoms or electrocardiogram abnormalities were reported in 9 % (95 % CI 4–21) and 14 % (95 % CI 7–26), respectively. Elevation in liver function tests or blood glucose abnormalities were reported in 7 % (95 % CI 2–20) and 4 % (95 % CI 1–17), respectively. No deaths were attributed to olanzapine.

Limitations No studies were identified with a primary focus on evaluating safety, and the adverse effects reported in the included studies were heterogeneous.

Conclusions Most adverse events associated with olanzapine use in children less than 13 years of age are of minor clinical significance. These findings support the

Key Points

Olanzapine is frequently used in children less than 13 years of age for various psychiatric and behavioural conditions

The most commonly reported adverse effects associated with olanzapine in children less than 13 years of age are weight gain, sedation, and increased appetite

Use of olanzapine in children younger than 13 years appears safe

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exploration of olanzapine for the prevention of CINV in children in future trials.

1 Introduction

Olanzapine is an atypical antipsychotic agent that is approved for use in the USA in patients greater than 13 years of age with psychiatric conditions. There is currently no approved indication for its use in patients less than 18 years of age in Canada and Europe. Nevertheless, olanzapine is frequently prescribed off-label for the treatment of various psychiatric and behavioural disorders in children [1–4]. Adverse effects associated with olanzapine in adults include weight gain, sedation, extrapyramidal symptoms (EPS), abnormalities in liver function tests (LFTs) and increased blood glucose, prolactin, cholesterol and/or triglyceride concentrations [5]. Adolescents receiving olanzapine may be at increased risk of experiencing some of these adverse effects, including weight gain, increased body mass index, and elevated blood glucose, cholesterol, triglyceride and prolactin concentrations [6–8]. The adverse effect profile of olanzapine in younger children has not been described systematically.

Olanzapine has recently shown promising results for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) in adult cancer patients [9–13]. Its efficacy can be attributed to its activity at many of the receptor sites involved in the mediation of CINV, including serotonin and dopamine pathways. Despite advances in antiemetic strategies for paediatric cancer patients, children receiving chemotherapy continue to experience uncontrolled CINV, which may limit their quality of life and lead to associated clinical problems [14, 15]. Olanzapine may be a valuable option for the prevention and treatment of CINV in children on the basis of its success in adults.

There are currently no published studies evaluating the use of olanzapine for prevention or treatment of CINV in children. Before undertaking future trials to evaluate the use of olanzapine for CINV control in children, a review of the adverse effects reported with olanzapine use in young children would be useful. The objective of this study was to describe the adverse effects associated with olanzapine use in children less than 13 years of age, the age at which the use of olanzapine is off-label in the USA.

2 Methods

2.1 Search Strategy and Data Sources

With the assistance of a library scientist, we conducted electronic searches of the following databases: OVID MEDLINE (1946–May 21, 2014), EMBASE and EMBASE Classic (1947–week 20, 2014), Cochrane Central Register of Controlled Trials (2005–April 2014), Web of Science (accessed May 21, 2014), and Scopus (accessed May 21, 2014). The search was completed in September 2013 and updated May 21, 2014. The complete search strategy is presented in Supplementary Table 1 (online resource 1). The search was limited to studies including infants, children and adolescents and those published in English. There was no restriction by study design. Reference lists of pertinent publications, including review articles, were searched to ensure all relevant articles meeting our inclusion criteria were included.

2.2 Study Selection

The following inclusion criteria were applied to the studies identified: (1) the population included patients younger than 13 years of age (either results were reported separately for patients younger than 13 or the mean or median age of participants was less than 13 years); (2) the study described adverse effects associated specifically with the use of olanzapine; and (3) the dose of olanzapine used or, in the case of poisoning where the dose ingested was not able to be determined, a blood olanzapine concentration was reported. The exclusion criteria were (1) not published in English, (2) conference abstracts or proceedings, (3) not a primary study (for example, reviews and editorials), (4) adverse effects not described, (5) specific results for olanzapine not reported separately from those of other medications, (6) population did not consist of children younger than 13 years of age or the mean or median age of participants was $\geq$13 years, and (7) duplicate studies. Duplicate studies were identified electronically using EndNote X7.1 (Bld 7705; Thomson Reuters); one reviewer (JF) reviewed all citations with the same title and/or authors to ensure removal of duplicate publications. Papers describing infants who were exposed to olanzapine in utero or via breast milk were also excluded.

The titles and abstracts of all studies identified were screened by two reviewers (JF and LD). Primary articles which described the use of olanzapine in children in the title and/or abstract were selected for full-text screening. Studies that proceeded to full-text screening were reviewed by two individuals (JF and LD). All discrepancies were discussed, and final inclusion of studies was based on agreement of both reviewers. An inter-rater reliability analysis using the Kappa statistic was performed to determine consistency among screeners (SAS Institute Inc.; Cary, NC, USA).

Study designs included randomized controlled trials, prospective single-blind, open-label, and naturalistic studies, retrospective reviews, case series and case reports.

Table 1 Characteristics of included studies

Author	Year of pub	Study design	Risk of bias in measurement of adverse effects	*N*	Mean age ± standard deviation (range)	Diagnosis	Mean olanzapine dose ± standard deviation (range)	Duration of olanzapine treatment
Hollander [17]	2006	RCT	Moderate	6	9.25 ± 2.9 years (6–14.8 years)	Pervasive developmental disorder	10 ± 2.04 mg/day (7.5–12.5 mg/day)	8 weeks
Shaw [18]	2006	RCT	Low	13	12.8 ± 2.4 years (6–17 years)	Childhood-onset schizophrenia	18.1 ± 4.3 mg/day (5–20 mg/day)	8 weeks
Wozniak [19]	2009	Prospective, open-label comparison	Moderate	17	10.2 ± 2.6 years (6–17 years)	Bipolar disorder	8.6 ± 3.4 mg/day (olanzapine group) (7.5–12.5 mg/day)	8 weeks
Fido [21]	2008	Prospective, open-label	Moderate	40	12.2 ± 2.2 years (7–17 years)	Autism	7.5 mg/day (5–10 mg/day)	13 weeks
McCracken [20]	2008	Prospective, open-label	Moderate	12	11.33 ± 2.35 years (7–14 years)	Tourette syndrome	11.3 ± 5.6 mg/day (2.5–20 mg/day)	6 weeks
Quintana [22]	2007	Prospective, open-label	Moderate	16	12.9 ± 2.48 years (8–17.9 years)	Schizophrenia	6.8 ± 6.41 mg/day (female participants) 8.33 ± 4.51 mg/day (male participants) (2.5–20 mg)	9 weeks
Milin [23]	2006	Prospective, open-label	Moderate	10	12.6 ± 2.02 years (10–15 years)	Asperger disorder	8.25 mg/day (5–15 mg/day)	12 weeks
Mozes [24]	2006	Prospective, open-label comparison	Low	12	11.5 ± 1.64 years (9–14 years)	Childhood-onset schizophrenia	8.18 ± 4.41 mg/day (2.5–20 mg/day)	12 weeks
Sethi [33]	2006	Prospective, open-label	High	6	Median 9 years (5–13 years)	Sydenham chorea	5.8 mg/day (5–10 mg/day)	3–4 months
Biederman [25]	2006	Prospective, open-label comparison	Moderate	15	5 ± 0.8 years (4–6 years)	Bipolar disorder	6.3 ± 2.3 mg/day (1.25–10 mg/day)	8 weeks
Stephens [26]	2004	Prospective, open-label	Moderate	10	9.9 ± 1.7 years (7–13 years)	Tourette syndrome	14.5 mg/day (1.25–20 mg/day)	8 weeks
Mozes [27]	2003	Prospective, open-label	Moderate	9	12.5 ± 1.13 years (11–14 years)	Childhood-onset schizophrenia	15.56 ± 4.64 mg/day (10–20 mg/day)	10 weeks
Ross [28]	2003	Prospective, open-label	Moderate	19	10.5 ± 2.4 years (6–15 years)	Childhood-onset Schizophrenia	5.1 ± 2.2 mg/day (week 3) 6.1 ± 3.6 mg/day (week 6) 7.7 ± 4.1 mg/day at (3 months) 9.3 ± 4.7 mg/day (6 months) 10.4 ± 3.5 mg/day (1 year)	Up to 1 year
Kemner [29]	2002	Prospective, open-label	Moderate	25	Mean 11.22 years (6.4–16.6 years)	Pervasive developmental disorder	10.7 mg/day (2.5–20 mg/day)	12 weeks

Table 1 continued

Author	Year of pub	Study design	Risk of bias in measurement of adverse effects	*N*	Mean age ± standard deviation (range)	Diagnosis	Mean olanzapine dose ± standard deviation (range)	Duration of olanzapine treatment
Frazier [30]	2001	Prospective, open-label	Moderate	23	10.3 ± 2.9 years (5.4–14.7 years)	Acute mania	9.6 ± 4.3 mg/day (2.5–20 mg/day)	8 weeks
Malone [31]	2001	Prospective, open-label comparison	High	6	8.5 ± 2.4 years (4.9–11.8 years)	Autism	7.9 ± 2.5 mg/day (5–10 mg/day)	6 weeks
Sholevar [32]	2000	Prospective, open-label	High	15	9.4 ± 1.99 years (6–13 years)	Childhood-onset schizophrenia	4.8 mg/day (2.5–5 mg/day)	Mean 11.3 days
Turkel [35]	2013	Retrospective review	High	16	1.7 ± 0.67 years (0.58–2.8 years)	Delirium	4.81 ± 5.76 mg/day (0.5–23 mg/day)	Mean 39 ± 41.4 days (range 2–151 days)
Turkel [34]	2012	Retrospective review	High	78	10.8 ± 4.9 years (1–18 years)	Delirium	10 mg/day (0.625–60 mg/day)	Mean 26.5 days (range 1–132 days)
Taskiran [53]	2013	Case report	N/A	1	7.5 years	Pervasive developmental disorder	15 mg/day	2 months
Bozkurt [37]	2010	Case report	N/A	1	11 years	Catatonia	5 mg/day	Not reported
Herguner [54]	2010	Case report	N/A	1	6 years	Autistic disorder	2.5–7.5 mg/day	Not reported
Ferreira Maia [38]	2007	Case report	N/A	1	10 years	Bipolar disorder	15 mg/day	Not reported
Emiroglu [39]	2006	Case report	N/A	1	8 years	Bipolar disorder	15 mg/day	6 months
Beresford [41]	2005	Case report	N/A	1	4.25 years	Schizophreniform disorder	8.75 mg/day (↓ to 3.75 mg/day after 1 month)	Not reported
Chungh [40]	2005	Case report	N/A	1	12 years	Bipolar disorder and mild mental retardation	2.5 mg/day	2 days
Courvoisie [43]	2004	Case report	N/A	1	7 years	Attention deficit hyperactivity disorder, bipolar disorder, and oppositional defiant disorder	2.5 mg/day	Approx. 9 months
Ercan [42]	2004	Case report	N/A	1	12 years	Schizophrenia	5–15 mg/day	Not reported
Boachie [44]	2003	Case series	N/A	4	11 years (10–12 years)	Anorexia nervosa	2.5 mg/day	Not reported
Sheikh [45]	2002	Case report	N/A	1	10 years	Acute agitation and attention deficit hyperactivity disorder	2.5–7.5 mg/day	15 days
Mehler [47]	2001	Case report	N/A	1	12 years	Anorexia nervosa	5 mg/day	Not reported

Table 1 continued

Author	Year of pub	Study design	Risk of bias in measurement of adverse effects	*N*	Mean age ± standard deviation (range)	Diagnosis	Mean olanzapine dose ± standard deviation (range)	Duration of olanzapine treatment
Nguyen [46]	2001	Case report	N/A	1	10 years	Attention deficit hyperactivity disorder	5 mg/day	Several months (specific time frame not reported)
Bengi Semerci [36]	2000	Case report	N/A	1	9 years	Tourette disorder	5 mg/day, increased to 10 mg/day after one week	Not reported
Chang [48]	2000	Case series	N/A	3	10.3 years (9–12 years)	Acute mania	2.5–5 mg/day	1–3 months
Lavid [49]	1999	Case reports	N/A	2	9.5 years (9–10 years)	Stuttering	1.25–2.5 mg/day	2–5 months
Krishnamoorthy [51]	1998	Case series	N/A	5	9.2 years (6–11 years)	Psychiatric disorder	7.5 mg/day (2.5–10 mg/day)	14–52 days
Malek-Ahmadi [50]	1998	Case report	N/A	1	8 years	Hyperactivity and aggressive behaviour	5–7.5 mg/day	Not reported
Horrigan [52]	1997	Case reports	N/A	2	9.5 years (9–10 years)	Bipolar disorder, mental retardation, and autistic behaviour	5–20 mg/day	Not reported
Hail [56]	2013	Case report (overdose)	Not applicable	1	6 years	Not applicable	75–100 mg	Not applicable
Tanoshima [55]	2013	Case report (overdose)	Not applicable	1	1.4 years	Not applicable	20–50 mg	Not applicable
Lankheet [57]	2011	Case report (overdose)	Not applicable	1	2.3 years	Not applicable	Reported 30 mg Estimated based on levels 115–230 mg	Not applicable
Kochhar [58]	2002	Case report (overdose)	Not applicable	1	12 years	Not applicable	210 mg	Not applicable
Bond [61]	1999	Case report (overdose)	Not applicable	1	6 years	Not applicable	10 mg	Not applicable
Bonin [60]	1999	Case report (overdose)	Not applicable	1	1 year	Not applicable	Unknown (level = 340 ng/mL)	Not applicable
Catalano [59]	1999	Case report (overdose)	Not applicable	1	1.5 years	Not applicable	30–40 mg	Not applicable
Chambers [63]	1998	Case report (overdose)	Not applicable	1	9 years	Not applicable	100 mg	Not applicable
Yip [62]	1998	Case report (overdose)	Not applicable	1	2.5 years	Not applicable	7.5–15 mg	Not applicable

N number, *RCT* randomized-controlled trial

Included studies were divided into those evaluating the use of olanzapine at usual recommended doses and studies focusing on overdose with olanzapine. Studies administering olanzapine at usual doses were divided into prospective versus non-prospective studies; only prospective studies were considered for synthesis.

2.3 Data Collection Process and Quality Assessment

Data were extracted from included studies by one reviewer (JF) and verified by an additional reviewer (LD). All included studies published by the same author(s) were reviewed to ensure data which may have been reported in multiple publications were included only once in our review and meta-analysis. Information gathered from each study included the study design, study aim, patient characteristics (sample size, age, gender, and indication for olanzapine use), dose of olanzapine used (in mg/kg/dose if reported or calculable and including the titration schedule if applicable), length of treatment with olanzapine, adverse effects monitored (including frequency and tools for monitoring), and adverse effects reported by the authors. Information was included on any adverse effects reported by the authors with a focus on those effects for which a proportion of patients who experienced the adverse effect was reported or could be calculated. Information was also gathered for changes from baseline in safety parameters which were statistically or clinically significant, including laboratory values monitored, with a focus on those values falling outside the normal range reported for age. Where available, information was collected for comparative groups when studies included either a placebo or different medication arm. Additional information was gathered for those articles describing olanzapine overdose, including the olanzapine blood concentration (if reported), other medications ingested, clinical presentation, and treatment and follow-up.

An effort was made to contact one author via e-mail to obtain more detailed information regarding adverse effects described in a supplementary table which was no longer available electronically. A response was not received. The available information related to adverse effects from this article was incorporated into the review and meta-analysis [18].

The risk of bias of included studies other than case reports was assessed independently by two reviewers (JF and LD) using a modified tool initially developed to describe the quality of prognostic studies [16]. Discrepancies were discussed and the final assessment was assigned on the basis of the agreement of both reviewers. A focus was placed on the risk of bias in outcome measurement, which may have most influenced adverse effect reporting. Each study was rated as having a low, medium, or high risk of bias in measurement of adverse effects.

The cumulative reported incidence of adverse effects that were not included in the meta-analysis (see below) but that were evaluated in at least three prospective studies was calculated.

2.4 Meta-Analysis

The proportion of patients who were reported to have experienced adverse effects which were assessed objectively [e.g. change in body weight, change in laboratory values, echocardiogram (ECG) abnormalities and EPS] or which have been reported to be commonly observed in adolescents (weight gain and sedation) were synthesized using Review Manager (RevMan Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The meta-analysis was limited to prospective studies including randomized controlled trials and open-label studies; retrospective reviews, case series and case reports were not included in this analysis since identification and measurement of adverse effects in these studies were subject to a high risk of bias. Outcomes were synthesized if at least two studies reported data on that outcome. Data were synthesized using proportions of children reported in each study to have experienced the adverse effect in question. Since proportions were not distributed normally, syntheses were conducted using the natural logarithm of the proportion as the outcome. Differences in mean proportion based on study design were evaluated using χ^2; $p < 0.05$ was considered to be significant.

3 Results

Figure 1 depicts the studies identified, screened, deemed eligible for inclusion and ultimately included in this review. A total of 4,238 articles were identified during the literature search. After abstract and title screening, 191 full-text articles were reviewed. Of these, 47 studies met inclusion criteria: 38 studies (17 prospective studies) evaluated olanzapine at usual recommended doses and nine studies described olanzapine overdose. Agreement between reviewers for inclusion of articles was almost perfect [kappa = 0.97, 95 % confidence interval (CI) 0.93–1.00]. Table 1 describes the characteristics of all the included studies.

3.1 Therapeutic Use of Olanzapine: Prospective Studies

The risk of bias in outcome measurement in the included studies is summarized in Table 1 and is highly variable. Safety assessment was a secondary outcome in all included

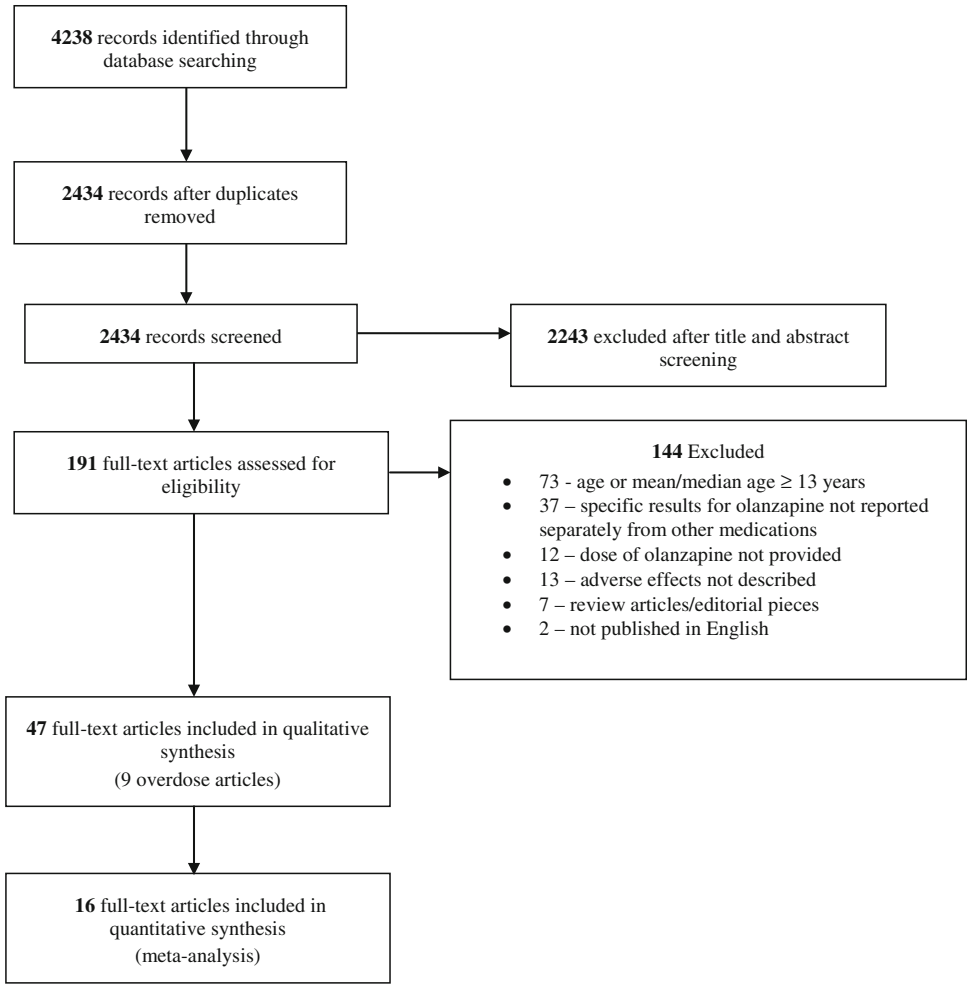

Fig. 1 Literature search flowchart

studies; some relied exclusively on spontaneous reporting of adverse effects during the period of time that olanzapine was administered, while others relied on specific tools to screen for specific possible adverse effects. Supplementary Table 2 (online resource 2) summarizes the information gathered from the randomized controlled trials (2) [17, 18], prospective studies (15) [19–33], and retrospective reviews (2) [34, 35].

A total of 254 patients, aged 4–17.9 years, participated in the included prospective studies. The indication for olanzapine use was for treatment of a psychiatric, developmental, or behavioural disorder. The duration of olanzapine use ranged widely (11.3 days to over 1 year), but the majority of studies (13/17) reported durations between 6 and 12 weeks. The dose of olanzapine used in the studies was often titrated on the basis of efficacy and patient tolerability and ranged from 1.25 to 20 mg daily. The olanzapine dose range was not reported in one study.

Twenty patients were reported to have withdrawn from the olanzapine arms of the prospective studies. Adverse effects attributed to olanzapine prompted the withdrawal of seven patients. Four patients withdrew because of weight gain, while the following adverse effects prompted the withdrawal of a further three patients: increased appetite (one patient), tremor (one patient), and increased appetite and hand tremor (one patient).

Data regarding sedation (12 studies), weight gain (seven studies), EPS (12 studies), ECG abnormalities (five studies), LFT abnormalities (three studies) and blood glucose abnormalities (three studies) were synthesized. The number of studies which reported the proportion of patients with other laboratory value abnormalities [i.e. elevations in plasma prolactin (one study), cholesterol (one study) and/or triglyceride concentrations (no studies)] was too few to permit synthesis.

The findings of the meta-analysis are summarized in Table 2 and Fig. 2. There was no difference in mean proportion between randomized controlled studies and other prospective studies ($p > 0.05$). Sedation and weight gain were reported in 48 % (95 % CI 0.35–0.67) and 78 % (95 % CI 0.63–0.95) of children, respectively. Other

Table 2 Synthesized adverse effects associated with olanzapine in young children*

Adverse effect	Number of studies	Number of children evaluated	Mean proportion (%)	95 % confidence interval
Blood glucose abnormalities [23, 28, 30]	3	43	4	1–17
Electrocardiogram abnormalities [18, 23, 26, 29, 31]	5	64	14	7–26
Extrapyramidal symptoms [17, 18, 21–24, 26–31]	12	180	9	4–21
Liver function test abnormalities [18, 27, 30]	3	45	7	2–20
Sedation [17–21, 25–27, 30–32]	12	191	48	35–67
Weight gain [17, 20, 27, 29–32]	7	96	78	63–95

* Studies included for synthesis were prospective studies that reported adverse effects which were assessed objectively or which have been reported to be commonly observed in adolescents. Studies excluded from synthesis were retrospective reviews, case series, and case reports

adverse effects reported to be more common in adolescents were less common in children less than 13 years of age. Abnormalities in blood glucose and LFT results were less commonly reported: 4 % (95 % CI 1–17) and 7 % (95 % CI 2–20), respectively.

EPS was evaluated using tools such as the Abnormal Involuntary Movement Scale (AIMS), Tardive Dyskinesia Rating Scale, Barnes Akathisia Score, and Simpson Angus Scale. EPS was reported in 9 % (95 % CI 4–21) of children. Of the four studies in which EPS was observed [21, 22, 24, 29], symptoms of EPS were immediately reversed after treatment with benztropine in one study, and a second reported that this adverse effect disappeared after patients' olanzapine doses were decreased [22, 29]. The other two studies do not provide details of the EPS symptoms or their management.

ECG was obtained in 64 children at baseline and during olanzapine therapy, and abnormalities were reported in 7 % (95 % CI 7–26). Three studies reported the details of ECG abnormalities. One patient had multiple atrial premature complexes and was deemed fit to continue receiving olanzapine treatment after consultation with cardiology [18]. In the second study, two patients experienced ECG abnormalities which were not thought to be caused by olanzapine [23]. One patient had sinus tachycardia thought to be a result of agitation; the second had apparent ventricular hypertrophy at the baseline assessment which resolved over the course of the study. Kemner et al. [29] observed ECG abnormalities in four patients which were not deemed to be clinically relevant or which were transient. None of these seven patients exhibited QTc prolongation.

Table 3 summarizes the cumulative reported incidence of adverse effects that were not included in the meta-analysis. Of these adverse effects, cold or flu-like symptoms, constipation, other gastrointestinal problems, and headache were most commonly reported.

No fatal events attributed to olanzapine were reported.

3.2 Therapeutic Use of Olanzapine: Retrospective Reviews

Two retrospective reviews were included in this review, both of which are summarized in Table 1 and Supplementary Table 2. These reviews included a total of 94 patients aged 0.6–18 years receiving olanzapine for the treatment of delirium. Patients included in these studies received olanzapine for anywhere from 1 to 151 days at doses ranging from 0.5 to 60 mg/day. In both studies, only one patient was reported to have experienced dystonia, which resolved when the olanzapine dose was decreased. No cardiac arrhythmias, EPS, or metabolic syndrome-related adverse effects were reported. No fatal events attributed to olanzapine were reported.

3.3 Therapeutic Use of Olanzapine: Case Reports and Case Series

Supplementary Table 3 (online resource 3) summarizes the data collected from case reports and case series which met inclusion criteria [36–54]. The age of the 30 patients included in these reports ranged from 4.25 to 12 years. Similar to the previously described studies, most patients received olanzapine for the management of behavioural or psychiatric conditions. The olanzapine dose administered in these reports ranged from 1.25 to 20 mg daily. The treatment duration, reported only by nine of the 19 authors, ranged from a few days to several months. Similar to the findings of the meta-analysis, weight gain (15 patients) and sedation (six patients) were commonly reported. Two authors each reported a single case of a serious potential adverse effect potentially associated with olanzapine use: catatonia and neuroleptic malignant syndrome (NMS) [37, 40]. Olanzapine was not felt to be the causal factor for catatonia by the authors of the first study as this patient did not present with the usual expected symptoms associated with antipsychotic-induced catatonia

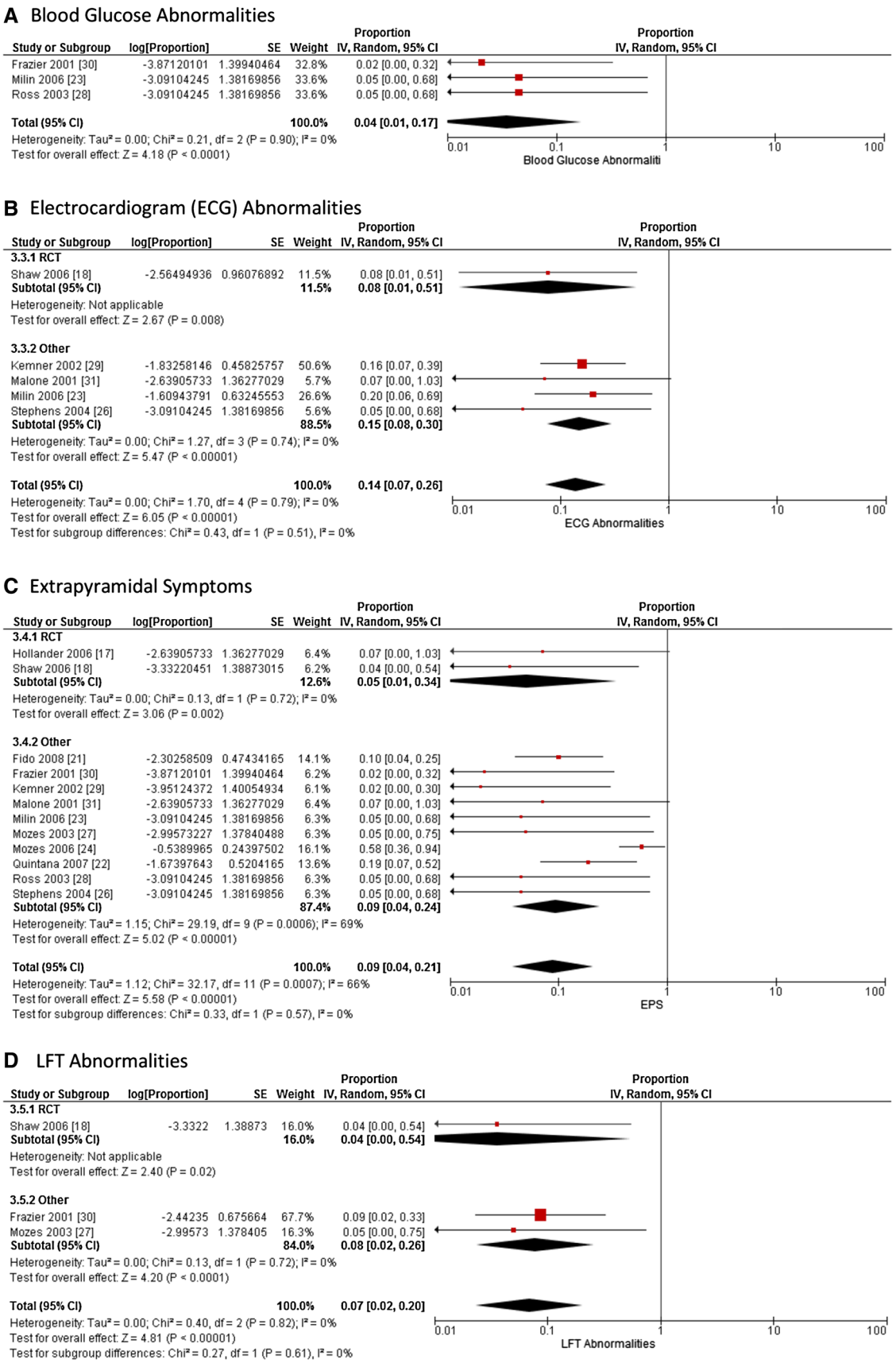

Fig. 2 Forest plots

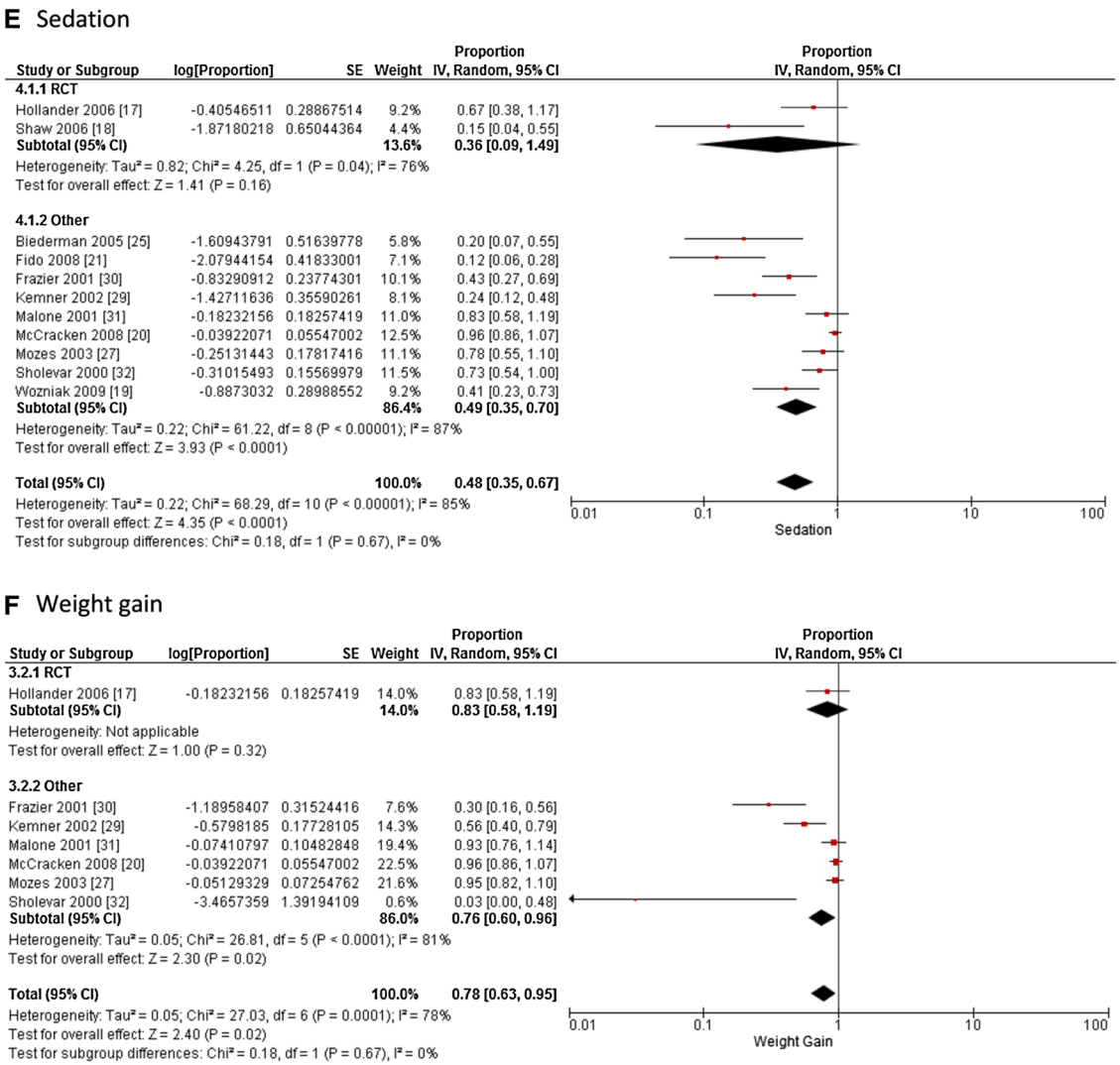

Fig. 2 continued

(dystonia, tremor, tardive dyskinesia, and/or fever). The patient who experienced olanzapine-associated NMS also experienced NMS following the administration of other atypical antipsychotics (risperidone and quetiapine). After all antipsychotics were discontinued, NMS symptoms resolved without long-term complications.

3.4 Olanzapine Overdose/Poisoning: Case Reports

Data extracted from the case reports of olanzapine overdose for nine patients are summarized in Supplementary Table 4 (online resource 4) [55–63]. Patients ranged in age from 1 to 12 years, and the olanzapine doses ingested ranged from 7.5 to 100 mg. The ingested dose was unknown for one patient; however, an olanzapine blood concentration was reported as 340 ng/mL 5 h post-ingestion. The olanzapine blood concentration was reported for an additional six patients (11–888 ng/mL) and varied depending on the timing of the concentration in relation to ingestion of olanzapine. For comparison, plasma olanzapine concentrations usually range from 5 to 75 ng/mL in adults receiving therapeutic doses [64]. The most frequent adverse effects associated with olanzapine overdose were drowsiness/lethargy/somnolence (8/9 patients), agitation/combativeness (7/9 patients) and tachycardia (6/9 patients). There were no fatal events attributed to olanzapine. Only one patient had sequelae at follow-up: a 9-year-old, 29-kg boy who ingested 100 mg of olanzapine had a "slight" upper extremity tremor at 13 days post-ingestion, which had improved significantly from the patient's initial presentation. There was no further follow-up for this patient.

Table 3 Summary of adverse effects associated with olanzapine administration reported in all included prospective studies* and which were excluded from synthesis

Adverse effect	Number of studies evaluating or reporting adverse effect	Total number of patients evaluated	% reported incidence
Akathisia [24, 26, 29, 30]	4	70	9 (6/70)
Anxiety [19, 25, 26]	3	42	2 (1/42)
Cold/flu-like symptoms [17, 19, 25]	3	38	29 (11/38)
Constipation [17, 18, 26]	3	29	24 (7/29)
Dry eyes/nose/mouth [19, 25, 26, 31]	4	48	8 (4/48)
Gastrointestinal problems [19, 25, 30, 31]	4	61	25 (15/61)
Headache [17, 19, 25, 26]	4	48	25 (12/48)
Hypersalivation [18, 25, 29]	3	53	15 (8/53)
Urinary adverse effects [18, 19, 25, 31]	4	51	8 (4/51)

* Cumulative reported incidence of adverse effects that were not included in the meta-analysis but that were evaluated in at least three prospective studies. These adverse effects were not synthesized in the meta-analysis because they are either not measured objectively or have not been reported to be commonly observed in adolescents

4 Discussion

In this systematic review, we found that the most common adverse events attributed to olanzapine were weight gain and sedation. Potentially serious adverse events were either not attributed to olanzapine and/or were reversible. No deaths were attributed to olanzapine in children. Consequently, neither the incidence of reported adverse effects nor their clinical severity presents barriers to the future evaluation of olanzapine for the prevention of CINV in young children.

We identified 47 studies that reported adverse effects associated with olanzapine in 387 children younger than 13 years of age. In order to accurately describe the contribution of olanzapine to adverse events, randomized controlled trials are the best design. However, only two included studies were randomized, which makes it more difficult to attribute the adverse events reported to olanzapine specifically. Although of lesser quality than randomized controlled trials, the prospective studies included in this review reported important and detailed information about adverse effects experienced by patients.

Synthesis was completed for those adverse effects objectively evaluated or most commonly reported in adolescents: ECG abnormalities, EPS, LFT abnormalities, blood glucose abnormalities, sedation and weight gain.

Mirroring the experience in adolescents, olanzapine-associated sedation and weight gain were commonly reported. However, blood glucose and LFT abnormalities were fairly uncommon. With respect to weight gain, it is important to note that patients included in the studies where weight gain was reported received olanzapine for at least 6 weeks. There appears to be a temporal relationship between use of olanzapine and weight gain, with risk increasing with duration of treatment. The most significant increase in weight (mean 12.8 kg) was reported for patients taking olanzapine for 1 year [65]. These results are not surprising considering the numerous reviews that describe the association between olanzapine and weight gain [6, 66] in older children.

Although concerning when they do occur, serious adverse effects associated with olanzapine seem to be uncommon. Nevertheless, it is important that children, parents and care-providers are taught to recognize the symptoms of EPS and NMS before a course of olanzapine is initiated.

The retrospective reviews of olanzapine use in young children provided an opportunity to observe the use of olanzapine in unique populations since they included patients as young as 7 months of age and receiving doses of olanzapine up to 60 mg daily. However, because of their retrospective design, very little detailed information regarding adverse effects associated with olanzapine were available, and attributing causality of the reported adverse effects is challenging. Nevertheless, the adverse effects reported in the retrospective reviews are reassuring considering the wide variability in patient age and olanzapine dose in these studies.

Although little high quality information could be gathered from the case reports included, they provide examples of the use of olanzapine in children younger than 13 years at therapeutic doses. Case reports describing the symptoms and management of children after olanzapine overdose provide a description of the extremes of dose-related olanzapine toxicity in very young children. Of importance, eight of the nine patients in the case reports included made a complete recovery after overdose and no long-term complications were reported for these patients. Meli et al. [67] recently described the acute toxicity profile of four atypical antipsychotic agents, including olanzapine, in

young children, using poison centres data. Specific doses of olanzapine ingested or blood concentrations were not reported by the authors; therefore, this study was excluded from our review. Nevertheless, the authors report a "toxic dose" threshold of 0.4 mg/kg, above which patients were noted to experience ataxia and somnolence. The most commonly reported symptom associated with olanzapine intoxication was minor reduction in vigilance (defined as a Glasgow Coma Score of >9). Of note, no patients were reported to have experienced QTc prolongation or EPS.

It is important to note that in considering the use of olanzapine in paediatric cancer patients, none of the studies included in this review administered the drug concurrently with chemotherapy. Consequently, nothing is known about the potential for interactions with chemotherapy or paediatric cancer supportive care drugs, or whether there are unique toxicities in this particular patient population. We are cautious regarding our ability to extrapolate the findings of this systematic review to the use of olanzapine in paediatric cancer patients since our findings may not be applicable to paediatric cancer patients who receive olanzapine for CINV control. Patients described in the studies included in this systematic review often received olanzapine over a number of weeks and the doses were usually titrated to an optimal dose. Children receiving olanzapine for the prevention of CINV would receive the medication over no more than several days while they receive blocks of chemotherapy. We cannot be certain that patients would tolerate a dose that has not been titrated. However, it is possible that sedation and weight gain may actually be viewed in a positive light in children receiving chemotherapy that is otherwise associated with anorexia and weight loss. Future feasibility or early phase studies are required to evaluate the safety of olanzapine in paediatric oncology patients.

The strength of this report is the systematic review of published reports of the adverse effects of olanzapine in young children. This knowledge is important to allow and plan future trials of olanzapine. The adverse effects identified in this review should be specifically monitored in prospective trials conducted in paediatric cancer patients.

Potential limitations to this systematic review must be considered. No studies were conducted specifically in this age group with a primary focus on evaluating safety. For this reason, less stringent inclusion/exclusion criteria were applied when determining study eligibility in our systematic review so as to capture all potential adverse effects reported as secondary outcomes. The heterogeneity of the adverse effects reported in the included studies limited our ability to synthesize the incidence of many possible adverse effects of olanzapine use. However, we believe that the summary of case reports of the therapeutic use of olanzapine as well as case reports of poisoning provide information regarding possible rare or dose-related toxicities. We acknowledge that case reports and case series may be subject to publication bias. There are additional limitations associated with the study inclusion/exclusion criteria chosen. Based on our age restriction and by only including studies where the mean or median age was less than 13 years, we may have missed descriptions of the experience of those patients younger than 13 years included in studies where the mean or median age exceeded 13 years. Although our literature search was comprehensive, only articles published in English were included and we may have missed relevant publications printed in other languages.

5 Conclusions

Overall, the use of olanzapine in children younger than 13 years appears relatively safe when it is administered at doses ranging from 2.5 to 20 mg and titrated to patient tolerability. Adverse effects such as sedation and weight gain may not be a large concern when used for short periods of time in paediatric cancer patients. On the basis of these findings and the drug's success as an antiemetic agent in adult cancer patients, future exploration of the efficacy of olanzapine for the prevention and/or treatment of CINV in children is warranted. Such evaluations should use rigorous methods and involve the use of validated paediatric tools for the assessment of nausea in order to determine efficacy. Standardized and, when possible, objective approaches should be used to evaluate the safety of olanzapine in paediatric cancer patients who may receive this medication for CINV.

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