Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

# Optimal Use Report

CADTH

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## A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia

*Supporting Informed Decisions*

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

**The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.**

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## Contributors from CADTH

**Tarun K. Ahuja, PhD**
Research Officer

**Chris Cameron, BSc, EngDip, MSc**
Health Economist

**Changhua Yu, MD, MSc**
Research Officer

**Nancy Robertson**
Knowledge Exchange Officer

**Janice Mann, MD**
Knowledge Exchange Officer

**David Kaunelis, MLIS**
Information Specialist

**Sumeet R. Singh, BScPhm, MSc, RPh**
Manager, Clinical Research

**Samantha Verbrugghe, BSc**
Research Assistant

**Kristen Moulton**
Research Assistant

**Janet Crain**
Manager, Knowledge Exchange

**Doug Lentz**
Project Manager

# Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Expert Review Committee

**Dr. Lisa Dolovich, Chair**
Research Director and Associate Professor, Department of Family Medicine, McMaster University;
Ambulatory Care Pharmacotherapy Specialist and Associate Director, Centre for Evaluation of Medicines, St. Joseph's Healthcare Hamilton

**Dr. Mike Evans, Vice-Chair**
Director, Patient Self-Management and Knowledge Support Centre for Effective Practice, Department of Family and Community Medicine, and Associate Professor, University of Toronto;
Director, Health Media Lab, Li Ka Shing Knowledge Institute, St. Michael's Hospital;
Staff Physician, Toronto Western Hospital

## Members

**Dr. Michael Allen**
Associate Professor,
Director, Evidence-based Programs, Continuing Medical Education,
Dalhousie University

**Dr. James L. Silvius**
Associate Professor, University of Calgary;
Senior Medical Director,
Seniors' Health and Living Options,
Alberta Health Services

**Dr. Scott Klarenbach**
Associate Professor, Department of Medicine, Division of Nephrology,
University of Alberta;
Fellow, Institute of Health Economics

**Dr. Adil Virani**
Director, Pharmacy Services, Fraser Health Authority;
Associate Professor, Faculty of Pharmaceutical Sciences, University of British Columbia

**Mr. Panos Petrides**
Public Member

**Ms. Cathy MacNutt**
Public Member

## Specialist Expert Members

**Dr. William G. Honer**
Professor of Psychiatry,
University of British Columbia;
Scientific Director, BC Mental Health & Addictions Research Institute;
Director, Centre for Complex Disorders

**Dr. Richard Williams**
Professor, Department of Psychiatry, University of British Columbia;
Adjunct Professor, Department of Psychology, University of Victoria;
Director of Schizophrenia Services, Royal Jubilee Hospital, Victoria

**Dr. Gary Remington**
Professor of Psychiatry, Head of Schizophrenia Program, Faculty of Medicine, University of Toronto;
Director, Medication Assessment Clinic & Deputy Director of Research and Education, Schizophrenia Program, Centre for Addiction and Mental Health

**Dr. Heather Milliken**
Associate Professor and Director of Continuing Medical Education, Department of Psychiatry, Dalhousie University;
Nova Scotia Early Psychosis Program

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# ABBREVIATIONS

| | |
|---|---|
| **AAP** | atypical antipsychotics |
| **AMI** | amisulpride |
| **APD** | antipsychotic drugs |
| **AE** | adverse event |
| **AIMS** | Abnormal Involuntary Movement Scale |
| **ANCOVA** | analysis of covariance |
| **ARI** | aripiprazole |
| **BA(R)S** | Barnes Akathisia Rating Scale |
| **BPRS** | Brief Psychiatric Rating Scale |
| **CGI** | Clinical Global Impression |
| **CGI-I** | Clinical Global Impression — Improvement |
| **CGI-S** | Clinical Global Impression — Severity |
| **CI** | confidence interval |
| **CLZ** | clozapine |
| **DIEPSS** | Drug-induced Extrapyramidal Symptoms Scale |
| **DSM-III** | Diagnostic and Statistical Manual of Mental Disorders (3rd Edition) |
| **DSM-IV** | Diagnostic and Statistical Manual of Mental Disorders (4th Edition) |
| **EPS** | extrapyramidal symptoms |
| **ESRS** | Extrapyramidal Symptoms Rating Scale |
| **ESRS-T** | Extrapyramidal Symptoms Rating Scale — Total |
| **GAF** | Global Assessment of Functioning scale |
| **HRQoL** | health-related quality of life |
| **ITT** | intention to treat |
| **LDL** | low-density lipoprotein |
| **LSM** | least squares mean |
| **OLZ** | olanzapine |
| **PANSS** | Positive and Negative Syndrome Scale |
| **PANSS-T** | Positive and Negative Syndrome Scale —Total score |
| **PANSS-N** | Positive and Negative Syndrome Scale — Negative score |
| **PANSS-P** | Positive and Negative Syndrome Scale — Positive score |
| **QoL** | quality of life |
| **QUET** | quetiapine |
| **RCT** | randomized controlled trial |
| **RIS** | risperidone |
| **RR** | relative risk |
| **SAE** | serious adverse event |
| **SANS** | Scale for the Assessment of Negative Symptoms |
| **SAPS** | Scale for the Assessment of Positive Symptoms |
| **SA(R)S** | Simpson-Angus Scale |
| **SD** | standard deviation |
| **SE** | standard error |
| **SUL** | sulpiride |
| **TAP** | typical antipsychotics |
| **WDAE** | withdrawal due to adverse event |
| **WMD** | weighted mean difference |
| **ZIP** | ziprasidone |

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# 1 INTRODUCTION

Optimizing drug-related health outcomes and the cost-effective use of drugs is a goal of the Canadian Agency for Drugs and Technologies in Health (CADTH). Where possible, CADTH builds on existing applicable Canadian and international initiatives and research.

CADTH goals are achieved through three main approaches:

- Identifying evidence-based optimal use in the prescribing and use of specific drugs
- Identifying gaps between clinical practice, then proposing evidence-based interventions to address these gaps
- Supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- The former Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) Advisory Committee (CAC) and the former Advisory Committee on Pharmaceuticals (ACP), which include representatives from the federal, provincial, and territorial health ministries and related health organizations
- The Drug Policy Advisory Committee (DPAC)
- The DPAC Optimal Use Working Group (OUWG)
    - DPAC and its OUWG were formed following the selection of this report's topic
- The COMPUS Expert Review Committee (CERC)
- Stakeholder feedback.

## 1.1 The COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office, and three or more Specialist Experts appointed to provide their expertise in recommending optimal use for one or more specific topics. For topics in the area of mental health, four specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, effecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members, including Public Members, are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature, and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective used by CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

# 2 ISSUE

CAC and ACP have identified atypical antipsychotics (AAPs) for schizophrenia — specifically, high-dose and combination therapy — as being a priority topic for optimal practice initiatives, based on the following criteria:

- Large deviations from optimal utilization (overuse or underuse)
- Size of patient populations
- Impact on health outcomes and cost-effectiveness
- Benefit to multiple jurisdictions
- Measurable outcomes
- Potential to effect change in prescribing and use.

## Schizophrenia

Schizophrenia is a chronic, recurrent mental illness that requires lifelong treatment[1] and is associated with symptoms that include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and amotivation.[2]

Patients with schizophrenia are at an increased risk for numerous other medical illnesses, suicide, substance abuse, homelessness, unemployment, and premature death.[3] Worldwide prevalence has been estimated at 0.5% to 1.5%[4] of the general population, and in Canada in 2004, prevalence was estimated at about 1% of the population or 234,305 people.[5,6]

Diagnostic criteria for schizophrenia are currently based on the latest revisions of the World Health Organization International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV).[7] For a diagnosis of schizophrenia, the DSM-IV requires that two or more of the following symptoms be present for a significant portion of one month or more: delusions, hallucinations, disorganized speech, catatonic behaviour, or negative symptoms.[7]

Symptoms of schizophrenia can be classified by different symptom domains, including positive or negative.[4] Positive symptoms include hallucinations and delusions, while negative symptoms include affective flattening, loss of interest, and alogia.[8]

The total financial burden of schizophrenia in Canada was estimated to be C$6.85 billion in 2004.[9] The annual direct health care and non-health costs were estimated at C$2.02 billion (2004 data) with acute (23%) and non-acute (38%) hospital care accounting for the majority of these costs.[9]

## Management of Schizophrenia

Antipsychotic medications form the cornerstone of treatment for schizophrenia, as they target the characteristic symptoms of the disease.[4] The underlying principles for the administration of pharmacotherapy include the individualization of medication (including patient preferences), simple medication regimens, appropriate dosing, regular evaluation of response and adverse events,[3] and short- and long-term clinical efficacy, safety, and tolerability.[1]

Although there have been important developments in this area over the last 40 years, about one-third of people with schizophrenia still have a poor response to antipsychotic medications.[7] Surveys of prescribing practices in the United Kingdom (UK) showed that the use of doses higher than those usually recommended is commonly encountered, when antipsychotic agents

are used either alone or in combination with another antipsychotic medication.[7] Although combination therapy with two antipsychotic agents is not recommended in current clinical management guidelines,[3] with the debatable exception of clozapine-based combination therapy,[7] it appears this practice is not uncommon.[7,10] Two longitudinal studies from the United States (US) reported that 9.5% to 22.0% of patients with schizophrenia received two antipsychotic agents concurrently,[11,12] and the proportion of patients treated with more than one AAP increased from 3.3% in 1999 to 13.7% in 2004.[11] Data from British Columbia indicate that the rate of antipsychotic polypharmacy increased between 1996, when an estimated 28% of patients discharged from hospital were on polypharmacy, and 2000, when the number was 45%. For patients using clozapine, the rate of polypharmacy increased from 22% in 1996 to 53% in 2000.[13] Reasons identified for this increasing prevalence include the use of as-required (PRN) medication and the gradual switch (bridging) from one antipsychotic to another, as well as the combination of two antipsychotic medications to achieve greater therapeutic response when there has been an unsatisfactory response to a single antipsychotic.[7] Overall, prevalence rates of antipsychotic polypharmacy range from 4% to 58%,[10] and rates up to 69%[13] have been reported, depending on treatment setting and patient population.

## Technology Description — Atypical Antipsychotics

Most existing antipsychotic therapies fall into one of two classes. The typical antipsychotics (TAP; also known as conventional antipsychotics or neuroleptics) are of the first-generation antipsychotic class. The atypical antipsychotics (AAP) are of the second-generation antipsychotic class.

Seven AAPs are currently available in Canada: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Two other AAPs, asenapine and iloperidone, were recently approved in the US, while sulpiride and amisulpride are available in the European Union (Table 1).

**Table 1:** List of Atypical Antipsychotics available in Canada and US

| Generic Name | Trade Name | Dose Range | Definition of High Dose[†] | Manufacturer |
|---|---|---|---|---|
| Aripiprazole | Abilify | 10–15 mg/day | >30 mg/day | Bristol-Myers Squibb |
| Asenapine* | Saphris | 10 mg/day (5 mg bid) | >10 mg/day | Schering-Plough |
| Clozapine | Clozaril | 300–600 mg/day | >600 mg/day[¶] | Novartis |
| Olanzapine | Zyprexa, Zypexa Zydis | 5–10 mg/day | >20 mg/day | Eli Lilly |
| Olanzapine*[‡] | Zyprexa Relprevv | 150–300 mg/2 weeks | >300 mg/ 2 weeks (405 mg/ 4 weeks) | Eli Lilly |
| Iloperidone* | Fanapt | 12–24 mg/day (administered 6–12 mg, bid) | >24 mg/day | Titan Pharmaceuticals |
| Paliperidone | Invega | 6–12 mg/day | >12 mg/day | Janssen-Ortho |
| Paliperidone injection[‡] | Invega Sustenna | 39–234 mg/month | >234 mg/month | Janssen-Ortho |
| Quetiapine | Seroquel | 300–800 mg/day | >800 mg/day | AstraZeneca |
| Quetiapine | Seroquel XR | 400–800 mg/day | >800 mg/day | AstraZeneca |
| Risperidone | Risperdal Risperdal M-Tab | 4–6 mg/day | >6 mg/day[§] | Janssen-Ortho |

| **Table 1:** List of Atypical Antipsychotics available in Canada and US | | | | |
|---|---|---|---|---|
| **Generic Name** | **Trade Name** | **Dose Range** | **Definition of High Dose†** | **Manufacturer** |
| | | | | |
| Risperidone injection‡ | Risperdal Consta | 25–50 mg/2 weeks | >50 mg/2 weeks | Janssen-Ortho |
| Ziprasidone | Zeldox | 120–160 mg/day | >160 mg/day | Pfizer |

* Approved by the US Food and Drug Administration, but not available in Canada.
† Based on maximum recommended doses according to the product monograph, unless otherwise indicated.
‡ Long-acting injectable agent
§ Based on expert opinion. Maximum recommended dose according to product monograph is 16 mg per day.
¶ Based on expert opinion. Maximum recommended dose according to product monograph is 900 mg per day.

# 3 OBJECTIVES

The objective of this study was to identify and appraise the clinical evidence pertaining to use of AAP combination therapy and high-dose treatment strategies in adolescents and adults with schizophrenia.

## 3.1 Project Overview

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. The CAC and ACP provide advice and guidance regarding topic identification. The OUWG, formed after topic identification, will provide advice and guidance throughout the process, through to supporting intervention and evaluation tools. CERC provides expert advice and recommendations on the topic area regarding the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.

This report represents the systematic review toward developing optimal use recommendations for the prescribing and use of combination and high-dose treatment strategies involving AAPs for schizophrenia.

## 3.2 Research Questions

1. What is the comparative clinical effectiveness (including clinical benefits and harms) of using combination therapy with AAPs (including the use of another AAP or a TAP as the other agent) compared with AAP monotherapy for the treatment of adolescents and adults with schizophrenia for whom treatment with a single AAP or TAP at recommended doses is inadequate?
2. What is the comparative clinical effectiveness (including clinical benefits and harms) of using high-dose AAP therapy compared with standard dose AAP therapy for the treatment of adolescents and adults with schizophrenia for whom treatment with an AAP or TAP at recommended doses is inadequate?

The population of interest for this review was adolescents (age 13 to 17 years) and adults (age 18 years and older) with schizophrenia (though studies may include patients with schizoaffective disorder) as defined by DSM-IV or ICD-10, including the first episode of schizophrenia, acute phase or chronic phase, inadequately managed with one or more AAPs at recommended doses.

A complete list of agents and comparators that were assessed is provided in the project protocol and outlined in Table 1. The newly approved AAPs lurasidone (trade name Latuda) and iloperidone (trade name Fanapt) were approved by the US Food and Drug Administration for treatment of schizophrenia[14,15] after this project was initiated. As a result, they were not included in the analysis. For the purposes of this assessment, high doses of AAPs were defined as outlined in Table 1.

# 4 METHODS

When possible, CADTH builds on existing applicable Canadian and international initiatives and research. The first phase of the research process was to conduct a literature search for existing systematic reviews or guidance on AAP combination and high-dose use. National Institute for Health and Clinical Excellence (NICE) guidelines (2009),[7] a Drug Effectiveness Review Project (DERP) report (2010),[16] Canadian Psychiatric Association (CPA) guidelines (2004),[3] American Psychological Association (APA) guidelines (2004 and 2009),[17,18] and other systematic reviews on AAP combination therapy[19-30] and on high-dose AAPs[31] were identified and assessed. None of these reports sufficiently addressed the tabled research questions; therefore, a systematic review of the primary literature was conducted.

The methodology for the systematic review is presented in detail in the project protocol.[32] The full literature search strategy is presented in Appendix 1. The following databases were searched via the OVID interface: MEDLINE (1950– ), MEDLINE In-Process & Other Non-Indexed Citations, Embase (1980– ), PsycINFO (1967– ), and The Cochrane Central Register of Controlled Trials. A parallel search was run in the CINAHL database via EBSCO. PubMed was also searched to capture additional citations not found in MEDLINE. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were each AAP drug name plus more general terms (e.g., atypical antipsychotics, second-generation antipsychotics), schizophrenia, schizoaffective disorder, drug combinations, and drug dosage. Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs) or controlled clinical trials. Retrieval was not limited by publication year, but was limited to the English or French language. The Internet was searched to identify unpublished (grey) literature from websites and databases of health professional associations, health technology assessment agencies, and related entities. Bibliographies of selected studies were also reviewed. Literature alerts were monitored after completion of the primary search in June 2010. Studies published after June 2010 that met our inclusion criteria were not included in meta-analyses; however, sensitivity analyses were performed to ensure results were not significantly changed (data not reported). Manufacturers of the agents considered in this review were provided the opportunity to submit unpublished data.

Studies were selected independently by two reviewers based on criteria developed a priori, with discrepancies resolved through consensus, or the judgment of a third reviewer if agreement could not be reached.

## 4.1 Selection Criteria

Studies were included if they met all of the following inclusion criteria and none of the exclusion criteria:

## 4.2 Inclusion criteria

Population

- Adolescents (13 to 17 years old) or adults (≥ 18 years old) with schizophrenia or schizoaffective disorder (including the first episode of schizophrenia, acute phase or chronic phase) inadequately controlled with one or more antipsychotic (atypical or typical) monotherapy regimens.

Interventions

- Combinations consisting of one of the AAPs listed in Table 1 at a dose lower than or equal to the definition of high dose, with one or more other antipsychotic drugs (atypical or typical), or
- AAP monotherapy at high doses (as defined in Table 1 above).

Comparators

- AAP or TAP monotherapy at any dose
- Combinations of antipsychotic drugs at any dose.

Outcomes

- Members of CERC identified outcomes of interest a priori. A compiled list of all outcomes identified was circulated to CERC members to rate the importance of each outcome on a 9-point scale: 1–3, not important; 4–6, important; and 7–9, critical. An outcome was analyzed in the review if the mean score was between 4 and 9. Included symptoms of schizophrenia (Positive and Negative Syndrome Scale [PANSS], Brief Psychiatric Rating Scale [BPRS], Clinical Global Impression — Improvement [CGI-I], Clinical Global Impression — Severity [CGI-S]), response rate, cognition, withdrawals, and serious adverse events. The outcomes of interest and their importance as rated by CERC are provided in Appendix 2. Background information on the psychiatric symptom scales considered in this review is presented in Appendix 3.

Study Design

- RCTs (including parallel, crossover, placebo- or active-controlled).

## 4.3 Exclusion criteria

- A study with a mixed population with more than 15% of participants not diagnosed with schizophrenia or schizoaffective disorder, and/or no subgroup analysis reported for patients with schizophrenia or schizoaffective disorder
- Studies on first episode psychosis that is not specified as first episode schizophrenia
- Studies on schizophreniform disorder
- Studies on monotherapy comparisons between different AAPs, different TAPs, or between AAP and TAP at doses lower than the high-dose thresholds outlined in Table 1
- Studies comparing TAP monotherapy at a recommended dose with the same TAP at high dose
- Studies comparing TAP monotherapy at a recommended dose with a combination of the same or different TAP plus another antipsychotic
- Studies on combination therapy with an antipsychotic agent and non-antipsychotic agent (e.g., mood stabilizer)
- Studies published in languages other than French or English.

## 4.4 Quality Assessment and Data Extraction

Study quality was assessed using the Scottish Intercollegiate Guidelines Network (SIGN-50) checklist for RCTs.[33] Quality assessment was performed by one reviewer and verified by a second reviewer. Disagreements were resolved through consensus, or the judgment of a third reviewer if agreement could not be reached.

Data were extracted from included studies using templates designed a priori. Data were abstracted by one reviewer with verification by a second reviewer. Disagreements were resolved through consensus, or the judgment of a third reviewer if agreement could not be reached.

## 4.5 Data synthesis and analysis

Some included studies administered antipsychotic agents at fixed doses, while others allowed dose titration. Antipsychotic dosing was reported variably in the included trials that permitted dose titration: average dose during the study, mean endpoint dose, and median endpoint dose. Mean endpoint doses are reported in this review where available; otherwise, median endpoint values are reported. Average doses were considered only if no measure of endpoint dose was reported.

For continuous outcome measures, meta-analysis was performed using a random effects generic inverse variance approach. Mean differences from baseline to follow-up (with corresponding measures of uncertainty), or variations thereof, were abstracted for each treatment arm from all included studies for all continuous outcome measures of interest. Where standard deviations for change scores were not reported, the approach described by Abrams et al.[34] and Follett et al.[35] was used where possible to impute standard deviations. This approach is based on empirical estimation of correlation where sufficient baseline and follow-up data are available from other trials with complete information on means and standard deviations at baseline, follow-up, and for change scores to permit an informed selection of a correlation value. This practice was planned to be carried out for each relevant pairwise comparison of therapies. Unfortunately, there were rarely sufficient data available for this approach. Imputation was therefore usually performed under the assumption of a moderate correlation value of 0.5 for the change scores, or by direct transfer of a standard error from another study if it was considered to be sufficiently similar.

Dichotomous outcomes, such as serious adverse events and suicidality, were meta-analyzed using relative risk as the effect measure. Dichotomous categories were defined as “no event” or “one or more events.”

The degree of heterogeneity in meta-analyses was estimated using the $I^2$ statistic. Where heterogeneity was greater than 75%, the associated results were determined to be inappropriate for pooling and separate trial data were presented. Selected forest plots are presented in Appendix 4.

Subgroup analyses were performed, where possible, according to individual AAPs and by number of antipsychotic drugs (APDs) failed prior to the trial (i.e., ≥ 1, ≥ 2). Individual sensitivity analyses were conducted by including studies in adolescents, or by removing:

- Studies of poor quality
- Studies employing a crossover design
- Studies of less than three months’ duration
- Studies in which intention to treat (ITT) results were not reported

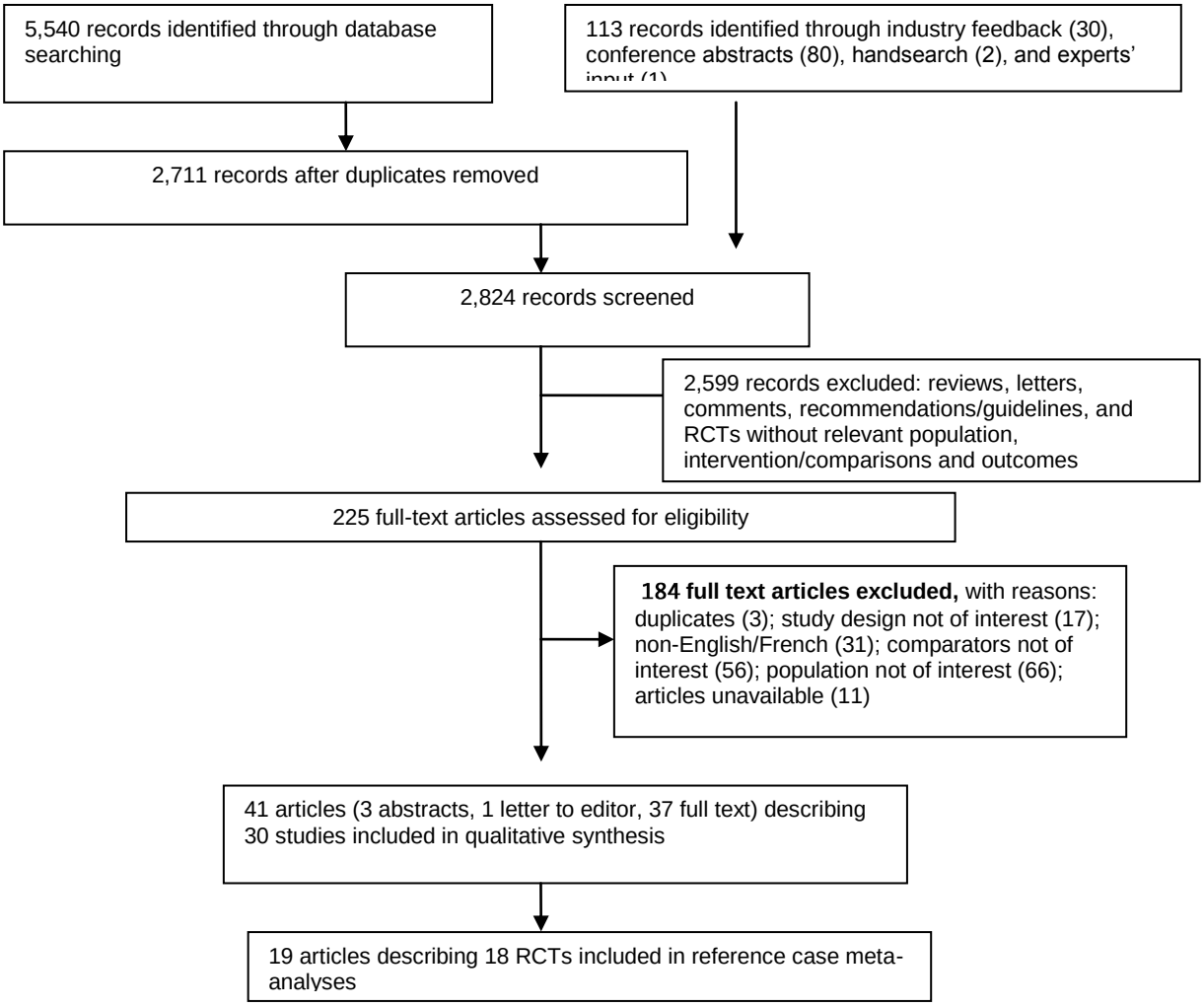
- Studies that examined agents not currently available in Canada
- Studies with clozapine (CLZ) dose less than 350 mg per day
- Studies reported only in conference/symposium abstracts.

# 5 RESULTS

## 5.1 Selection of Primary Studies

Figure 1 illustrates the selection process used to identify primary studies comparing AAP combination therapy with APD monotherapy as well as high-dose AAP therapy with standard-dose APD therapy in patients inadequately controlled on APD monotherapy. After removal of duplicates, a total of 2,824 citations were identified in the literature search. Of these, 2,599 citations were excluded, based on titles and/or abstracts. These consisted mainly of reviews, study designs other than RCTs, and studies in which comparators were not of interest. Full-text articles of the remaining 225 citations were assessed, and 41 articles representing 30 unique RCTs were included in the systematic review. The complete lists of included and excluded studies are presented in Appendices 6 and 7, respectively. In several instances, data from the same clinical trial were presented in multiple articles; these are outlined in Appendix 8. The publication with the longest duration of follow-up was used when analyzing data from such trials. Data from 19 articles describing 18 RCTs were included in the meta-analyses. A summary of studies not included in the reference cases is presented in Appendix 18.

Figure 1: PRISMA Diagram of Study Selection Results




## 5.2 Study Characteristics

Our systematic review included 41 articles representing 30 unique RCTs reported in 37 full-text articles,[36-72] three conference abstracts,[73-75] and one letter to the editor[76] (Table 2).

Add-on of an antipsychotic agent to existing CLZ monotherapy was the most common treatment strategy studied amongst the included RCTs (13 included articles[38,41,42,44-46,49,51,54,69,73-75] representing 12 RCTS). Addition of a non-CLZ APD to non-CLZ AAP monotherapy was only reported in one trial.[36] Eight RCTs[39,40,43,48,53,56-59,61,66,70,71,76] compared high-dose non-CLZ AAP strategies with standard-dose CLZ. Two trials[68,72] compared high-dose non-CLZ AAP strategies with standard-dose non-CLZ APDs. No trials were identified comparing non-CLZ combination therapy with CLZ monotherapy.

Of the studies, 57% were sponsored and/or funded by the pharmaceutical industry, 20% did not report funding sources, and the remaining studies were funded by alternate sources.

| **Table 2:** Summary of Study Characteristics | | |
|---|---|---|
| **Study Characteristics** | **Categories** | **Number (%) of Included Studies** |
| Publication status | Full texts | 37 (90.3) |
| | Abstracts | 3 (7.3) |
| | Other | 1 (2.4) |
| | Unique RCTs | 30 |
| Country | Multinational | 4 (13.3) |
| | Single country | 25 (83.3) |
| | Not reported | 1 (3.3) |
| Study design | Parallel RCTs | 29 (96.7) |
| | Crossover RCTs | 1 (3.3) |
| Sponsors or funding | Industry | 17* (56.7) |
| | Public funding | 7 (23.3) |
| | Not reported | 6 (20.0) |
| Publication year (range) | | 1992 to 2010 |
| Randomized sample size (range) | | 10 to 323 |
| Duration of study treatment (range in weeks) | | 6 to 52 |

RCTs = randomized controlled trials.
*Studies were considered sponsored or funded by industry if a pharmaceutical company was one of the funders, but not if it only provided study drugs.

Of 30 included RCTs, only one RCT[40] was conducted in adolescents (aged 10 to 18 years). Baseline duration of illness for the adult studies ranged from 7[52] to 22[46] years (weighted mean [SD] 15.6 [4.8]). Seventeen RCTs reported baseline PANSS scores ranging from 77.2 (SD: 11.9)[41] to 108.2 (SD: 15.7)[53] (weighted mean [SD] 88.35 [11.0]). The inclusion and exclusion criteria used in each study are presented in Appendix 9. While inclusion criteria such as age of participants were fairly consistent across trials (weighted mean [SD] 39.05 [3.8] years), there was some heterogeneity with regard to the inclusion and exclusion criteria in certain key areas such as comorbid disorders or suicidality. A broad range of antipsychotic doses was used in the included trials.

Definitions of inadequate control employed in studies and response to treatment are presented in Appendices 10 and 11, respectively. The primary population of interest for the current systematic review was patients with schizophrenia inadequately controlled with standard doses of AAP or TAP monotherapy. The definition of inadequate control of schizophrenia in most studies was based on Kane's criteria[77] or some modification thereof; i.e., patients had no or partial response to two to three antipsychotics based on PANSS or BPRS scores prior to trial. In most studies, patients had to be currently treated with an APD for a minimum of at least four to eight weeks with no concomitant APDs, and to have failed at least two previous trials of antipsychotic therapy. However, some RCTs included patients who failed at least one previous agent[36,50,58] or as many as three;[55,65] others required APD therapy for four to six months; and still others used more than one scale to assess symptom severity (PANSS, CGI, BPRS). In a small subset of studies, patients were reported as inadequately controlled with existing AAP therapy but had an unspecified treatment history.[54,72] Another scenario was that in which patients were treated with an AAP and would undergo a washout period with a placebo or a run-in period with an agent distinct from their pre-study medication (e.g., haloperidol) to demonstrate treatment resistance to pharmacotherapy.[78]

With respect to the interventions of interest, there were no RCTs that investigated the use of asenapine, iloperidone, or paliperidone. Common outcome measures included symptom scales (e.g., PANSS, BRPS, CGI), body weight, and adverse events. No evidence was available for relapse rate or clinical remission rate.

Table 3 provides further detail regarding baseline characteristics in the included studies. Complete study and patient characteristics are available in Appendices 12 and 13, respectively.

**Table 3:** Summary of Patient Characteristics

| **Patient Characteristics** | | **Range from All Included Studies** |
|---|---|---|
| Patient population | Adolescents (10–18 years old) | 1 RCT |
| | Adult (>18 years old) | 29 RCTs |
| Patients' mean age (years) | | 31 to 46* |
| Patents' gender (per cent male) | | 0% to 99.2% |
| Duration of schizophrenia/schizoaffective disorder (years) | | 7 to 27* |
| Percentage of patients withdrawing prematurely from study (%) | | 0% to 54% |
| Baseline PANSS | | PANSS total score (mean ± SD): 77.2±11.9 to 108.2±15.7 |
| Criteria for defining inadequate control (PANSS, CGI, BPRS) | | PANSS total score: 60 to 120;<br>BPRS total score: ≥ 35 to 45 or less than 20% decrease during antipsychotic treatment<br>CGI-S: ≥ 4 |

BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; CGI-S = Clinical Global Impression — Severity; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation.
* Not including adolescent study.[40]

## 5.3 Study Quality

Three RCTs[38,44,54] were rated as being of "good" quality, and the remaining 27 RCTs included in this review were assessed as being of "poor" methodological quality. The primary reasons for downgrading study quality were failure to describe an adequate method for allocation concealment, failure to use an ITT analysis, high rates of dropout (≥ 20%), and the differential use of concomitant medication between treatment arms. Assessment of the methodological quality of the three RCTs reported only as conference abstracts[73-75] was not possible. See Appendix 14 for more detail on the assessment of methodological quality for each included study.

## 5.4 Overview of Clinical Analysis

Where sufficient data and clinical homogeneity were present, pairwise meta-analyses were conducted for PANSS, BPRS, CGI, body weight, global assessment of functioning (GAF), metabolic outcomes, and harms such as severe adverse events and withdrawals due to adverse events. Nineteen articles[36,38,39,41,44,45,48,49,51,53,54,57,58,60,66,68-70,72] representing 18 RCTs were included in the reference case. Data from the remaining 22 articles (from 12 RCTs plus 10

duplicate reports)[37,40,42,43,46,47,50,52,55,56,59,61-65,67,71,73-76] were not pooled in the reference case, for the following reasons (see also Appendix 18):

- Data were published only in abstracts[73-75]
- Adolescent population[40]
- Mixed dosing strategies (i.e., polypharmacy where at least one agent was also given at high dose)[46,47,52]
- Comparison of one combination therapy with another combination[37,50]
- Duplicate data[42,43,55,56,59,62,64,67,71,76]
- Comparison of a high-dose AAP with another high-dose antipsychotic.[61,63,65]

One study comparing high-dose clozapine with high-dose haloperidol[63] was also not included in the reference case meta-analyses, as there were no similar studies with which it could be pooled.

All subgroup and sensitivity analyses specified in the protocol were conducted, with the exception of "specific APDs failed prior to the trial" and "severity of disease at baseline." These analyses were not performed, due to lack of data or inconsistencies in reporting amongst the included studies.

## 5.5 Clozapine-based antipsychotic combination therapy versus clozapine-monotherapy standard dose

Eleven RCTs published in 12 articles[38,41,42,44,45,49,51,54,69,73-75] (N = 619) compared CLZ-based combination therapy versus CLZ monotherapy in patients with schizophrenia inadequately controlled with standard-dose CLZ. Among these, six studies[39,41,44,46,69,75] were on the combination of risperidone (RIS) + CLZ; three RCTs[38,54,74] on aripiprazole (ARI) + CLZ; one[49] on amisulpride (AMI) + CLZ; one[51] on sulpiride (SUL) + CLZ; and one[73] on haloperidol (HAL) + CLZ. The mean daily dose of CLZ varied from 300 mg to greater than 680 mg. The mean daily dose of RIS ranged from 2.9 mg to 5.1 mg, while that of ARI ranged from 4 mg to greater than 15 mg. Trial duration ranged from six to 12 weeks. For detailed information on study characteristics, see Appendix 12.

Results from the reference case analyses are summarized in Table 4. Detailed information, including subgroup and sensitivity analyses, is presented in Appendices 4 and 5.

**Table 4:** Summary of Results from Reference Case Meta-analyses of Clozapine-Combination Therapy versus Clozapine Monotherapy

| Outcome | No. Trials | No. Pts | Effect Estimate (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| **Efficacy Outcomes** | | | | |
| PANSS — total*§ | 4 | 327 | Not pooled due to high heterogeneity | N/A |
| PANSS — positive*‡ | 4 | 327 | 0.23 (–0.97 to 1.43) | 75% |
| PANSS — negative*‡ | 4 | 327 | –0.34 (–1.07 to 0.39) | 26% |
| BPRS*§ | 2 | 114 | –0.88 (–4.32 to 2.55) | 56% |
| CGI-I*§ | 1 | 206 | –0.30 (–0.58 to –0.02) (WMD between groups at end point) | N/A |

| **Table 4:** Summary of Results from Reference Case Meta-analyses of Clozapine-Combination Therapy versus Clozapine Monotherapy | | | | |
|---|---|---|---|---|
| **Outcome** | **No. Trials** | **No. Pts** | **Effect Estimate (95% CI)** | **Heterogeneity ($I^2$)** |
| CGI-S*‡ | 5 | 424 | 0.04 (–0.22 to 0.30) | 63% |
| GAF*§ | 2 | 236 | –1.43 (–6.28 to 3.42) | 66% |
| Response rate†‡ | 6 | 426 | 1.35 (0.81 to 2.25) | 0% |
| Persistence with therapy†§ | 8 | 503 | 0.97 (0.92 to 1.02) | 0% |
| Quality of life (QLS scale[45])*§ | 1 | 30 | 0.30 (–5.93 to 6.53) | N/A |
| **Adverse Events** | | | | |
| Serious/severe adverse events†§ | 6 | 410 | 8.45 (1.03 to 69.54) | 0% |
| Withdrawals due to adverse events†§ | 5 | 380 | 1.68 (0.49 to 5.75) | 0% |
| Withdrawals (all-cause) †§ | 8 | 503 | 1.30 (0.78 to 2.17) | 0% |
| Hospitalization†§ | 1 | 68 | 3.00 (0.13 to 71.15) | N/A |
| Mortality (all-cause) †§ | 1 | 207 | Not estimable | N/A |
| **Adverse Events – EPS-Related** | | | | |
| Akathisia†§ | 3 | 251 | 3.41 (0.46 to 25.44) | 0% |
| EPS (number of patients with EPS)†§ | 2 | 235 | 2.25 (0.73 to 6.94) | N/A |
| EPS score (ESRS-T, DIEPSS)*§ | 2 | 130 | 0.18 (–0.77 to 1.13) | 0% |
| Parkinsonism†§ | 2 | 41 | 0.60 (0.08 to 4.54) | N/A |
| Tardive dyskinesia†§ | 1 | 28 | Not estimable | N/A |
| AIMS*‡ | 3 | 107 | 0.02 (–0.77 to 0.80) | 38% |
| BARS*§ | 3 | 107 | –0.29 (–0.79 to 0.20) | 51% |
| SAS*§ | 4 | 314 | –0.25 (–0.72 to 0.22) | 15% |
| **Adverse Events — Body Weight** | | | | |
| Body weight (kg)*‡ | 5 | 414 | Not pooled due to high heterogeneity | N/A |
| Weight gain (number of pts with weight gain) †‡ | 3 | 285 | 0.65 (0.16 to 2.61) | 0% |
| **Adverse Effects — Metabolic and Other** | | | | |
| Cholesterol — total*‡ (mmol/L) | 3 | 307 | –0.15 (–0.25 to –0.06) | 0% |
| Cholesterol — HDL*‡ (mmol/L) | 3 | 302 | –0.01(–0.08 to 0.06) | 30% |
| Cholesterol — LDL*‡ (mmol/L) | 3 | 300 | –0.20 (–0.34 to –0.07) | 6% |
| Triglycerides (mmol/L)*‡ | 3 | 303 | –0.21(–0.60 to 0.17) | 60% |
| FPG*‡ (mmol/L) | 4 | 342 | –0.12 (–0.54 to 0.31) | 24% |

**Table 4:** Summary of Results from Reference Case Meta-analyses of Clozapine-Combination Therapy versus Clozapine Monotherapy

| Outcome | No. Trials | No. Pts | Effect Estimate (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| Hyperglycemia[†‡] | 1 | 50 | 1.50 (0.48 to 4.68) | N/A |
| Prolactin (ng/mL)*[‡] | 6 | 188 | Not pooled due to high heterogeneity | N/A |
| Agranulocytosis[†§] | 1 | 61 | Not estimable | N/A |

AIMS = Abnormal Involuntary Movement scale; BARS = Barnes Akathisia Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression — Improvement scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale; EPS = extrapyramidal symptoms; ESRS-T = Extrapyramidal Symptoms Rating Scale total score; FPG = fasting plasma glucose; GAF = Global Assessment of Functioning; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N/A = not applicable; PANSS = Positive and Negative Symptom Scale; QLS = quality of life scale; SAS = Simpson-Angus Scale; WMD = weighted mean difference.

* WMD of change from baseline for combination minus monotherapy.
† Risk ratio (combination/monotherapy) for experiencing one or more events.
‡ Outcome was ranked as important by expert committee.
§ Outcome was ranked as critical by expert committee.

Regarding efficacy, there were no statistical differences between groups for any outcome, with the exception of CGI-I (based on one RCT [N = 206], WMD [95% CI]: –0.30 [–0.58 to –0.02]), where slightly better improvement was seen in the CLZ combination arm compared with CLZ monotherapy at the end of 16 weeks' treatment. For the majority of harms outcomes, there were no statistically significant differences between groups. Total cholesterol was statistically significantly lower with CLZ combination than CLZ monotherapy (based on three RCTs [N = 307], WMD [95% CI]: –0.15 [–0.24 to –0.06] mmol/L), as was low-density lipoprotein (LDL) cholesterol (based on three RCTs [N = 300], WMD [95% CI]: –0.20 [95% CI: –0.33 to –0.07] mmol/L). However, more serious adverse events occurred with CLZ combination therapy (11 of 216 patients) than CLZ monotherapy (0 of 194 patients), based on six RCTs (N = 410), RR (95% CI): 8.45 (1.03 to 69.54). Study level definitions of serious adverse events are presented in Appendix 15.

Meta-analyses with $I^2$ values above 75% (PANSS-T, body weight, and prolactin level) are not presented, although individual estimates are presented graphically in Figures A1.1, A1.32, and A1.41 of Appendix 4. The four studies that reported PANSS-T scores were inconsistent in their findings. One study[45] showed a small, statistically significant reduction with CLZ monotherapy (WMD [95% CI]: 5.70 [0.96 to 10.44]) relative to CLZ combination therapy; all patients included in this trial had a PANSS total ≥ 72 at baseline. Another study[41] revealed a small, statistically significant benefit with CLZ combination therapy (WMD [95% CI]: –4.70 [–6.84 to –2.56]); all patients had a PANSS total ≥ 60 at baseline in this trial. The other two studies[44,54] did not show a statistically significant difference between CLZ combination and CLZ monotherapy. The baseline PANSS-total for Honer et al.[44] was greater than 80, while no baseline psychiatric symptom score was reported for Fleischhacker et al.[54]

Five studies reported prolactin levels; three trials[45,48,51] reported statistically lower prolactin levels with CLZ monotherapy, while two trials[38,69] indicated a non-significant difference (see Figure A1.41 of Appendix 4). Heterogeneity was reduced to 63% when the two studies[41,69] that included a run-in period were removed.

In terms of body weight, four trials that compared RIS[44,45,69] or ARI[38] did not show a statistically significant difference between combination and monotherapy. However, one study[54] of patients

who had gained more than 2.5 kg on CLZ monotherapy prior to the start of the trial reported a significant difference in body weight reduction with ARI combined with CLZ, despite similar clozapine doses between arms. It is this study[54] that contributed to the high heterogeneity observed in the pooled analysis for this outcome.

More patients withdrew due to adverse events (WDAE) with CLZ combination therapy compared with monotherapy (8/200 versus 4/180), although the relative risk of WDAE was not statistically significant (five RCTs [N = 380], Figure A1.19 of Appendix 4). In addition, more patients experienced akathisia (six of 138 patients) with CLZ combination than CLZ monotherapy (zero of 113 patients); however, the relative risk was again not statistically significant (three RCTs [N = 251], Figure A1.24 of Appendix 4).

*Subgroup analyses*
In terms of the effect size and direction, the results from the majority of subgroup analyses were similar to those of the reference case analysis (see Table A1 of Appendix 5).

In subgroup analyses by agent, total cholesterol levels were lower for RIS+CLZ combination therapy than CLZ monotherapy (one RCT[44] [N = 68], WMD [95% CI] [mmol/L]: –0.15 [–0.25 to –0.05]), but not for ARI+CLZ combination therapy. However, LDL cholesterol levels were lower for ARI+CLZ (two RCTs [N = 269], WMD [95% CI]: –0.23 mmol/L [–0.36 to 0.10]), but not for RIS+CLZ compared with monotherapy. Prolactin levels were significantly higher with SUL+CLZ combination therapy versus CLZ monotherapy (one RCT[51] [N = 28], WMD [95% CI] [ng/mL]: 62.77 [37.17 to 88.38]), but not with ARI+CLZ (one RCT[38] [N = 62], WMD [95% CI] [ng/mL]: 11.65 (–23.34 to 46.63]). For RIS+CLZ compared with CLZ monotherapy, three studies[41,45,69] reported prolactin levels. Anil et al.[45] and Freudenreich et al.[41] reported a mean difference of 61 (95% CI, 46.95 to 75.05) and 27.5 (95% CI, 5.94 to 49.06), respectively, in favour of CLZ monotherapy. Weiner[69] found a nonstatistically significant mean difference of –15.23 (95% CI, –39.49 to 9.03) in favour of RIS+CLZ combination therapy. The pooled results are not presented due to a high level of heterogeneity. Agent-level subgroup analyses revealed that more patients experienced SAEs with ARI+CLZ compared with CLZ monotherapy (two RCTs[38,54] [N = 269], RR [95% CI]: 19.27 [1.14 to 324.53) but not RIS+CLZ therapy (two RCTs[44,45] [N = 98], RR [95% CI]: 3.00 [0.13 to 71.15]). No SAEs occurred in the trial[49] comparing AMI+CLZ combination therapy with SUL+CLZ.

Subgroup analyses based on the number of antipsychotic agents previously failed were performed. PANSS total and PANSS-positive scores were statistically significantly higher in CLZ combination compared with CLZ monotherapy in patients who failed three or more APDs (PANSS-total: one RCT[45] [n = 30], WMD [95% CI]: 5.7 [0.96, 10.44]); PANSS-positive: one RCT[45] [n = 30], WMD [95% CI] 2.40 [0.87 to 3.93]).

*Sensitivity analyses*
The majority of sensitivity analyses showed no difference in results in comparison with the reference case (see Table A1 of Appendix 5). However, when studies shorter than three months in duration were removed, body weight (kg) was statistically lower with CLZ combination therapy relative to monotherapy (two RCTs[54,69] [N = 376], WMD [95% CI]: –1.92 kg [–2.84 to –1.01]). When non-ITT trials were removed, prolactin level was higher with CLZ combination therapy (three RCTs[41,45,51] [N = 82], WMD [95% CI] [ng/mL]: 50.85 [27.09 to 74.6]).

When studies with mean CLZ dose < 350 mg/d were removed, the relative risks for WDAE, all-cause WD, SAE, and akathisia remained similar to the reference case.

## 5.6 Non-clozapine antipsychotic combination therapy versus non-clozapine monotherapy

One 16-week RCT[36] (n = 323) compared risperidone (RIS) or quetiapine (QUET) plus ariprazole (ARI) combination therapy with RIS or QUET + placebo in patients inadequately controlled on RIS or QUET monotherapy. No other studies comparing non-clozapine combinations with antipsychotic monotherapy were identified.

Reference case results are presented in Table 5. Detailed results, including subgroup analyses, can be found in Appendices 4 and 5.

**Table 5:** Summary of Results from the Trial Comparing Risperidone or Quetiapine + Aripiprazole with Risperidone or Quetiapine Monotherapy[36]

| Outcome | No. Pts Analyzed | Effect Estimate (95% CI) |
|---|---|---|
| **Efficacy Outcomes** | | |
| PANSS — total*§ | 310 | –0.10 (–2.59 to 2.79) |
| PANSS — positive*‡ | 310 | 0.50 (–0.40 to 1.40) |
| PANSS — negative*‡ | 310 | 0.10 (–0.84 to 1.04) |
| CGI-I*§ | 310 | –0.10 (–0.38 to 0.18) (MD between groups at endpoint) |
| CGI-S*‡ | 310 | 0.00 (–0.19 to 0.19) |
| Response rate†‡ | 310 | 1.01 (0.78 to 1.33) |
| Persistence with therapy†§ | 323 | 0.99 (0.86 to 1.15) |
| Quality of life (QLS scale[45])*§ | 310 | –1.10 (–4.06 to 1.86) |
| **Adverse Events** | | |
| Serious/severe adverse events†§ | 322 | 0.38 (0.17 to 0.85) |
| Withdrawals due to adverse events†§ | 322 | 0.51 (0.23 to 1.12) |
| Withdrawals (all-cause)†§ | 323 | 1.02 (0.74 to 1.41) |
| Suicidal ideation†§ | 322 | 0.08 (0.00 to 1.48) |
| Suicide (attempted)†§ | 322 | 0.30 (0.01 to 7.36) |
| Suicide (completed)†§ | 322 | Not estimable |
| Mortality (all-cause)†§ | 322 | Not estimable |
| **Adverse Events — EPS-Related** | | |
| Akathisia†§ | 322 | 0.82 (0.36 to 1.88) |
| EPS (number of pts with EPS, RR) †§ | 322 | 0.67 (0.35 to 1.28) |
| **Adverse Events — Body Weight** | | |
| Weight (kg)*‡ | 323 | 0.20 (–0.92 to 1.32) |
| Weight gain (number of pts with weight gain) †‡ | 323 | 1.41 (0.77 to 2.61) |
| **Adverse Effects — Metabolic and Other** | | |
| Cholesterol — total*‡ (mmol/L) | 253 | –0.05 (–0.13 to 0.03) |
| Cholesterol — HDL*‡ (mmol/L) | 253 | 0.05 (–0.04 to 0.14) |
| Cholesterol — LDL*‡ (mmol/L) | 252 | –0.03 (–0.09 to 0.04) |
| Triglycerides*‡ (mmol/L) | 175 | –0.21 (–0.6 to 0.18) |

**Table 5:** Summary of Results from the Trial Comparing Risperidone or Quetiapine + Aripiprazole with Risperidone or Quetiapine Monotherapy[36]

| Outcome | No. Pts Analyzed | Effect Estimate (95% CI) |
|---|---|---|
| FPG*‡ (mmol/L) | 175 | 0.03 (–0.26 to 0.32) |
| Prolactin (ng/mL)*‡ | 175 | –10.40 (–16.53 to –4.27) |

BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression — Improvement scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; EPS = extrapyramidal symptoms; FPG = fasting plasma glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MD = mean difference; N/A = not applicable; PANSS = Positive and Negative Symptom Scale; pts = patients; QLS = quality of life scale; RR = relative risk.

* Mean difference of change from baseline for combination minus monotherapy.
† Risk ratio (combination/monotherapy) for experiencing one or more events.
‡ Outcome was ranked as important by expert committee.
§ Outcome was ranked as critical by expert committee.

*Reference case analysis*
There were no statistically significant differences between groups for any efficacy-related outcomes for this comparison. In terms of harms, prolactin levels (MD [95% CI]: –10.40 ng/mL [–16.53 to –4.27]) showed a statistically significant decrease from baseline with combination therapy compared with monotherapy, and there were fewer serious adverse events in patients using combination therapy (RR [95% CI]: 0.38 [0.17 to 0.85]).

*Subgroup analyses*
Only one RCT[36] was included in this comparison, which presented data pooling the RIS and QUET groups. All-cause withdrawals and prolactin were the only outcomes of interest reported by individual agent. Results for prolactin remained statistically lower with combination therapy when ARI was added to RIS (N = 177, MD [95% CI] [ng/mL]: –16.80 [–26.64 to –6.96]), but not when ARI was added to QUET (N = 146, MD [95% CI] [ng/mL]: –3.16 [–6.94 to 0.62]) (see Figure A2.3 of Appendix 4). All-cause withdrawals were not significantly different in the reference case and remained non-significant when subgrouped by drug.

## 5.7 High-dose non-clozapine AAP therapy versus standard-dose clozapine

*Reference case analysis*
Eight RCTs presented in 14 publications[39,40,43,48,53,56-59,61,66,70,71,76] (N = 866) compared high-dose non-clozapine AAP therapy with standard-dose clozapine therapy in patients inadequately controlled with non-CLZ APDs. Of these, one study[40] comparing a high dose of OLZ with standard-dose CLZ was conducted in adolescents aged 10 to 18 years. The remaining seven trials were conducted in adults, of which two trials[60,66] compared high-dose RIS with standard-dose CLZ, and four RCTs, presented in six publications,[39,43,48,53,70,76] compared high-dose OLZ with standard-dose CLZ. One RCT, published in four articles,[56-58,71] compared both high-dose RIS and high-dose OLZ with standard-dose CLZ.

Results of the meta-analyses are shown in Table 6. Detailed information, including subgroup and sensitivity analyses, can be found in Appendices 4 and 5.

**Table 6:** Summary of Results from Reference Case Meta-analyses of High-Dose Non-clozapine Atypical Antipsychotics versus Standard-Dose Clozapine

| Outcome | No. Trials | No. Pts | Effect Estimate (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| **Efficacy Outcomes** | | | | |
| PANSS — total*§ | 6 | 668 | 2.09 (–2.71 to 6.90) | 59% |
| PANSS — positive*‡ | 6 | 668 | 0.93 (–0.40 to 2.27) | 32% |
| PANSS — negative*‡ | 6 | 668 | 0.47 (–1.41 to 2.34) | 75% |
| BPRS*§ | 2 | 379 | Not pooled due to high heterogeneity | N/A |
| CGI-I*§ | 1 | 40 | –0.30 (–2.26 to 1.66) (MD at endpoint) | N/A |
| CGI-S*‡ | 5 | 587 | 0.21 (–0.13 to 0.54) | 69% |
| GAF†§ | 1 | 40 | –7.50 (–12.83 to –2.17) | N/A |
| Response rate†‡ | 4 | 505 | 0.97 (0.84 to 1.14) | 0% |
| Persistence with therapy†§ | 7 | 770 | 0.95 (0.80 to 1.13) | 54% |
| **Adverse Events** | | | | |
| Serious/severe adverse events†§ | 1 | 68 | 0.98 (0.71 to 1.33) | N/A |
| Withdrawals due to adverse events†§ | 6 | 730 | 0.57 (0.34 to 0.96) | 0% |
| Withdrawals (all-cause) †§ | 7 | 770 | 0.98 (0.81 to 1.18) | 0% |
| Suicidal ideation†§ | 1 | 86 | 1.00 (0.06 to 15.48) | N/A |
| Suicide (completed) †§ | 1 | 86 | Not estimable | N/A |
| Mortality (all-cause) †§ | 1 | 273 | 1.02 (0.06 to 16.18) | N/A |
| **Adverse Events — EPS-Related** | | | | |
| Akathisia†§ | 1 | 176 | 0.88 (0.38 to 2.06) | N/A |
| EPS (number of pts with EPS) †§ | 2 | 327 | 2.17 (1.33 to 3.54) | 0% |
| EPS score (ESRS)*§ | 1 | 327 | 0.10 (–1.30 to 1.51) | 0% |
| Parkinsonism†§ | 2 | 262 | 0.65 (0.44 to 0.97) | 0% |
| Tardive dyskinesia†§ | 2 | 224 | 1.14 (0.45 to 2.89) | 0% |
| AIMS*‡ | 1 | 40 | 0.90 (–0.45 to 2.25) | N/A |
| SAS*§ | 1 | 40 | –0.80 (–2.03 to 0.43) | N/A |
| **Adverse Events — Body Weight (kg) ‡** | | | | |
| Body weight (kg)*‡ | 6 | 500 | 0.42 (–1.35 to 2.18) | 68% |
| Weight gain (number of pts with weight gain) †‡ | 3 | 323 | 0.70 (0.41 to 1.19) | 0% |
| **Adverse Effects — Metabolic and Other** | | | | |
| Cholesterol — total*‡ (mmol/L) | 3 | 110 | –0.16 (–0.47 to 0.16) | 0% |
| Triglycerides*‡ (mmol/L) | 2 | 34 | –0.82 (–1.65 to 0.01) | 0% |
| FPG (mmol/L)*‡ | 3 | 110 | 0.10 (–0.31 to 0.51) | 0% |

**Table 6:** Summary of Results from Reference Case Meta-analyses of High-Dose Non-clozapine Atypical Antipsychotics versus Standard-Dose Clozapine

| Outcome | No. Trials | No. Pts | Effect Estimate (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| A1C (%)*‡ | 1 | 22 | 0.03 (–0.32 to 0.38) | N/A |
| Hyperglycemia†‡ | 1 | 76 | 0.68 (0.25 to 1.82) | N/A |
| Prolactin (ng/mL)*‡ | 2 | 142 | 5.40 (1.08 to 9.73) | 0% |
| Agranulocytosis†§ | 3 | 456 | 0.29 (0.05 to 1.82) | 0% |

BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression — Improvement scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; EPS = extrapyramidal symptoms; FPG = fasting plasma glucose; GAF = Global Assessment of Functioning; MD = mean difference; N/A = not applicable; PANSS = positive and negative symptom scale; pts = patients.

* WMD of change from baseline for high dose minus standard dose.
† Risk ratio (high dose/standard dose) for experiencing one or more events.
‡ Outcome was ranked as important by expert committee.
§ Outcome was ranked as critical by expert committee.

There were no statistically significant differences in efficacy between groups except for GAF scores (one RCT[39] [N = 40], WMD [95% CI]: –7.50 [–12.83 to –2.17]), which were improved with standard-dose CLZ compared with high-dose AAPs. Data on BPRS from two trials[53,60] were not pooled due to high heterogeneity ($I^2$ >75%). One trial[60] [n = 273] reported significantly improved BPRS scores in the standard-dose clozapine arm compared with high-dose risperidone (WMD [95% CI]: 7.10 [3.65 to 10.55]). Patients included in this trial were required to have a baseline BPRS score greater than 60. In the other trial [n = 180],[53] BPRS score was greater than 45 at baseline, and no significant difference between high-dose olanzapine therapy and standard-dose clozapine was found (WMD [95% CI]: –1.20 [–5.43 to 3.03]). Individual trial data for BPRS are presented in Figure A3.8 in Appendix 4.

With respect to harms, there were no statistically significant differences between groups for most outcomes. Patients on high-dose non-CLZ AAPs had higher prolactin levels (two RCTs[53,70] [N = 142], WMD [95% CI] [ng/mL]: 5.40 [1.08 to 9.73]), and a higher incidence of EPS (two RCTs[60,70] [N = 327], RR [95% CI]: 2.17 [1.33 to 3.54]) compared with standard-dose CLZ. In contrast, use of high-dose non-clozapine AAPs was associated with fewer cases of Parkinsonism (two RCTs[53,66] [N = 262], RR [95% CI]: 0.65 [0.44 to 0.97]) as well as fewer WDAEs (six RCTs[48,53,58,60,66,70] [N = 730], RR [95% CI]: 0.57 [0.34 to 0.96]). There was no overlap between studies reporting total EPS incidence[60,70] and those reporting Parkinsonism,[53,66] allowing for this apparent discrepancy.

*Subgroup analyses*
In terms of the effect size and direction, the results from the majority of subgroup analyses were similar to those of the reference case analysis (see Table A3 in Appendix 5). Exceptions are outlined below.

In patients who had previously failed one or more APDs, PANSS-total (three RCTs[58,60,70] [N = 508], WMD [95% CI]: 6.17 [0.69 to 11.66]), PANSS-negative (three RCTs[58,60,70] [N = 508], WMD [95% CI]: 2.07 [0.21 to 3.93]) and PANSS-positive (three RCTs[58,60,70] [N = 508], WMD [95% CI]: 1.60 [0.11 to 3.09]) were all improved with standard-dose CLZ therapy relative to high-dose AAPs. In those studies with patients failing two or more APDs, PANSS-negative score was improved with non-CLZ high-dose therapy compared with CLZ standard dose (three RCTs,[39,53,66] [n = 306], WMD [95% CI]: –1.53 [–3.03 to –0.03]).

In the subgroup analysis by agent for PANSS-negative score, four RCTs compared high-dose OLZ with standard-dose CLZ. Two[53,58] (n = 259) did not report a statistically significant difference between agents, one[70] reported a significantly higher score in the high-dose OLZ arm (n = 68, MD [95% CI]: 4.60 [2.05 to 7.15]) and the fourth[39] (n = 40) reported a significantly lower score in the high-dose arm (MD [95% CI]: –2.70 [–4.28 to –0.58]). Data could not be pooled for this subgroup analysis due to high heterogeneity (see Figure A3.6 of Appendix 4). Three RCTs[58,60,66] compared high-dose RIS versus standard-dose CLZ for PANSS-negative; the pooled estimate revealed no significant difference between treatment arms (WMD [95% CI]: 1.25 [–0.18 to 2.68]).

When CGI-S was examined, statistically lower scores were found for the CLZ arm when compared with high-dose RIS therapy (based on two RCTs[60,66] [N = 359], WMD [95% CI]: 0.40 [0.01 to 0.79]) but not high-dose OLZ therapy (based on three RCTs[39,53,70] [N = 298], WMD [95% CI]: –0.02 [–0.39 to 0.34]) (see Figure A3.11 of Appendix 4).

Agent-level subgroup analyses for BPRS revealed statistically improved results with standard-dose CLZ when compared with high-dose RIS (one RCT[60] [N = 273], WMD [95% CI]: 7.10 [3.65 to 10.55]), but not high-dose OLZ (one RCT[53] [N = 180], WMD [95% CI] –1.20 [–5.43 to 3.03]) (see Figure A3.8 of Appendix 4).

Agent-level subgroup analysis indicated that weight was statistically significantly reduced with high-dose RIS therapy relative to clozapine (based on two RCTs[58,66] [N = 253], WMD [95% CI]: –1.71 kg [–3.05 to –0.36]), but not high-dose OLZ therapy (based on five RCTs[39,43,53,58,70] [N = 468], WMD [95% CI]: 1.78 kg
[–0.66 to 4.22]), compared with standard-dose clozapine. Agent-level subgroup analyses demonstrated that high-dose OLZ was associated with significantly fewer patients withdrawing due to adverse events compared with clozapine [four RCTs[48,53,58,70] [N = 310], RR [95% CI]: 0.36 [0.15 to 0.85]), but that high-dose RIS therapy was not (three RCTs[58,60,66] [N = 420], RR [95% CI]: 0.74 [0.39 to 1.41]) (see Figure A3.17 of Appendix 4). Additionally, high-dose RIS demonstrated a higher risk of EPS compared with CLZ [one RCT[60] [N = 270], RR [95% CI]: 2.14 [1.29 to 3.56]), but this was not the case for high-dose OLZ (one RCT[70] [N = 57], RR [95% CI]: 2.56 [0.39 to 16.67]) (see Figure A3.21 of Appendix 4).

When the number of previously failed APDs was one or more, CGI-S was lower for standard-dose CLZ therapy (two RCTs, N = 341, WMD [95% CI]: 0.60 [0.30 to 0.90]), but not significantly different when the number of failed APDs was two or more.

*Sensitivity analyses*
The majority of sensitivity analyses showed no difference in results in comparison to the reference case (see Table A3 in Appendix 5),with the exception that PANSS-negative was significantly lower with high-dose AAP therapy (three remaining RCTs[39,53,66] [N = 306], WMD [95% CI]: –1.53 [–3.03 to –0.03]) when studies not reporting ITT analyses were removed.

Sensitivity analyses removing trials with CLZ doses < 350 mg per day did not change the effect size for most outcomes compared with reference case analyses. However, unlike the reference case analysis, PANSS-positive was significantly higher with high-dose non-CLZ AAP compared with standard-dose CLZ therapy (three RCTs[39,58,60] [N = 443], WMD [95% CI]:1.68 [0.09 to 3.28]), as was BPRS [one RCT[60] [N = 273], WMD [95% CI]: 7.10 [3.65 to 10.55]). After studies with CLZ doses < 350 mg per day were removed, the significant difference in relative risk of WDAE found in the reference case was no longer apparent (RR [95% CI] 0.69 [0.37 to 1.31]). Four trials[39,53,60,70] [n = 581] reporting CGI-S remained after trials shorter than three months'

duration were removed, but could not be pooled due to high heterogeneity ($I^2$ > 77%). No statistically significant differences between treatments were found with the exception of one trial[60] [n = 273] where CGI-S was slightly higher in the high-dose AAP arm (WMD [95% CI]: 0.6 [0.29 0.91]).

## 5.8 High-dose non-clozapine AAP versus standard-dose non-clozapine APD

Two RCTs[68,72] (N = 173) compared high-dose non-clozapine AAP therapy with standard-dose non-clozapine APDs. One RCT[72] compared high-dose QUET with standard-dose QUET in patients who were inadequately controlled on 800 mg per day of QUET while the other[68] compared high-dose RIS with standard-dose haloperidol in patients who were inadequately controlled on an unspecified typical APD.[68] Results of the reference case meta-analyses are presented in Table 7. Detailed meta-analysis information including sensitivity and subgroup analyses are presented in Appendices 4 and 5.

**Table 7:** Summary of Results from Reference Case Meta-analyses of High-Dose Non-clozapine Atypical Antipsychotics versus Standard-Dose Non-clozapine Antipsychotic Drugs

| Outcome | No. Trials | No. Pts | Effect Estimate (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| **Efficacy Outcomes** | | | | |
| PANSS — total*§ | 2 | 173 | Not pooled due to high heterogeneity | N/A |
| PANSS — positive*‡ | 2 | 173 | Not pooled due to high heterogeneity | N/A |
| PANSS — negative*‡ | 2 | 173 | –0.13 (–1.12 to 0.86) | 0% |
| CGI-S*‡ | 1 | 131 | –0.10 (–0.61 to 0.41) | 0% |
| Response rate†‡ | 2 | 173 | 1.27 (0.65 to 2.47) | 44% |
| Persistence with therapy†§ | 2 | 173 | 1.07 (0.82 to 1.40) | 66% |
| **Adverse Events** | | | | |
| Serious/severe adverse events†§ | 1 | 131 | 1.47 (0.16 to 13.68) | N/A |
| Withdrawals due to adverse events†§ | 2 | 173 | 1.09 (0.27 to 4.42) | 0% |
| Withdrawals (all-cause) †§ | 2 | 173 | 0.64 (0.11 to 3.60) | 63% |
| Suicidal ideation†§ | 1 | 131 | 1.49 (0.06 to 37.37) | N/A |
| Suicide (attempted) †§ | 1 | 131 | Not estimable | N/A |
| Suicide (completed) †§ | 1 | 131 | Not estimable | N/A |
| Mortality (all-cause) †§ | 1 | 131 | Not estimable | N/A |
| **Adverse Events — EPS-Related** | | | | |
| EPS (number of pts with EPS) †§ | 2 | 173 | 0.70 (0.27 to 1.79) | 0% |
| Tardive dyskinesia†§ | 1 | 131 | 0.16 (0.02 to 1.52) | N/A |
| **Adverse Events — Body Weight** | | | | |
| Body weight (kg) *‡ | 2 | 173 | 1.28 (0.04 to 2.52) | 0% |
| Weight gain (number of pts with weight gain) †‡ | 1 | 131 | 4.40 (0.58 to 33.60) | N/A |
| **Adverse Effects — Metabolic and Other** | | | | |
| Cholesterol — total*‡ (mmol/L) | 1 | 100 | 0.08 (–0.19 to 0.35) | N/A |
| Cholesterol — HDL*‡ (mmol/L) | 1 | 100 | 0.02 (–0.05 to 0.09) | N/A |

**Table 7:** Summary of Results from Reference Case Meta-analyses of High-Dose Non-clozapine Atypical Antipsychotics versus Standard-Dose Non-clozapine Antipsychotic Drugs

| Outcome | No. Trials | No. Pts | Effect Estimate (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| Cholesterol — LDL*‡ (mmol/L) | 1 | 100 | –0.05 (–0.33 to 0.23) | N/A |
| Triglycerides*‡ (mmol/L) | 1 | 100 | 0.31 (–0.22 to 0.84) | N/A |
| FPG*‡ (mmol/L) | 1 | 131 | –0.06 (–0.47 to 0.35) | 0% |
| Prolactin (ng/mL) *‡ | 2 | 134 | –0.43 (–3.56 to 2.71) | 0% |

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; EPS = extrapyramidal symptoms; FPG = fasting plasma glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N/A = not applicable; PANSS = Positive and Negative Symptom Scale; pts = patients.

* WMD of change from baseline for high dose minus standard dose.
† Risk ratio (high dose/standard dose) for experiencing one or more events.
‡ Outcome was ranked as important by expert committee.
§ Outcome was ranked as critical by expert committee.

*Reference case analysis*
There were no statistically significant differences between groups in terms of efficacy or harm outcomes.

Data for PANSS-total and PANSS-positive from the two included studies[68,72] were not pooled, due to high heterogeneity. For PANSS-total, the trial[68] comparing high-dose RIS with standard-dose HAL found significantly greater improvement with high-dose RIS, while a trial[72] comparing high-dose QUET with standard-dose QUET did not find a significant difference. Similarly, PANSS-positive was significantly improved when high-dose RIS was compared with standard-dose HAL,[68] but not when high-dose QUET was compared with standard dose.[72]

*Subgroup and sensitivity analyses*
All subgroup and sensitivity analyses were similar to the reference case (see Appendix 5).

## 5.9 Evidence on clozapine-combination versus clozapine-combination AAP therapies

The current systematic review identified two studies that compared one clozapine-based combination therapy with another clozapine-based combination therapy.[50,55] Since the intervention strategies used in the two RCTs were different, data could not be pooled (see Appendix 18). In terms of PANSS score, CGI-S, and WDAE and all-cause withdrawals, no statistically significant differences between AMI+CLZ and QUET+CLZ or between RIS+CLZ and ZIP+CLZ were found in patients inadequately controlled on CLZ monotherapy (see Appendix 18).

## 5.10 Effect of AAP combination or high-dose AAP therapies on cognitive function

Data on cognition were sparse and heterogeneous, making meta-analyses unfeasible. No clear patterns were apparent regarding benefit or harm with either high-dose or combination therapies. For detailed cognition data by comparison, and further organized by MATRICS Consensus Battery domains,[79,80] see Appendix 16.

## 5.11 Additional Evidence on the Safety of Combination and High-Dose Therapy

The current systematic review focused on evidence from RCTs, which typically are unable to provide adequate information on drug safety. To address this gap, a review of safety evidence from observational studies is presented in Appendix 17.

### 5.12 Results from studies identified in literature alerts

The RCT literature search for the AAP project was performed on June 16, 2010. Monthly RCT alerts were maintained until May 2011. Four studies[81-84] meeting the inclusion criteria were identified via these alerts. Two studies[81,82] compared CLZ-based combinations with CLZ monotherapy. One[83] compared non-CLZ high-dose with non-CLZ standard-dose AAP. The fourth trial[84] compared CLZ augmentation with either aripiprazole or haloperidol. Sensitivity analyses incorporating the new data from the four trials did not significantly affect the results of the reference case analyses (data not shown).

# 6 DISCUSSION

Antipsychotic medication is an essential component in the treatment of patients with schizophrenia.[3] It has been suggested that AAPs are more effective than TAPs in the treatment of negative, cognitive, and depressive symptoms in patients with schizophrenia, although definitive studies and meta-analyses for these claims are lacking.[85-87] Convincing evidence has not been reported that shows a clear and consistent difference between AAPs and TAPs regarding reduction of positive symptoms, with the exception of clozapine for treatment-refractory patients.[88] About 30% of people with schizophrenia have a poor response to antipsychotic medications.[7] Clozapine is commonly recommended for treatment of patients who are inadequately controlled following trials with two different classes of antipsychotics, or who display persistent aggression or persistent suicidal thoughts or behaviour.[3] However, due to the safety concerns with clozapine, such as clozapine-induced agranulocytosis,[89,90] myocarditis,[91,92] and diabetes,[93,94] as well as a lack of response in a significant proportion (40% to 70%) of patients,[95] high-dose AAP or AAP combination therapy is often tried,[95-100] even though these strategies are not recommended in most current clinical practice guidelines.[3,7,10,13] CADTH's analysis of 2009 Ontario Public Drug Program utilization data showed that AAP combination therapy (AAP plus another AAP or TAP) accounted for 19% and high-dose AAP therapy for 4% of total active months of APD therapy in beneficiaries inferred to have schizophrenia.[101] Other estimates of high-dose and combination usage range widely, from approximately 5% to 50%, and are likely on the higher end for patients with schizophrenia who are inadequately controlled on standard-dose APD monotherapy.[7,11-13,102-104] The current systematic review explores whether high-dose or combination therapy with AAPs may be of benefit in patients with schizophrenia inadequately controlled on standard dose APD monotherapy.

### 6.1 Summary of Main Findings

We identified 30 RCTs that examined atypical antipsychotics agents used in high-dose and combination treatment strategies for patients with schizophrenia inadequately controlled on antipsychotic monotherapy. High-dose therapy was defined based on clinical expert opinion; for most agents, doses exceeding the Health Canada–approved maximum recommended dose were considered high dose. The exceptions were risperidone and clozapine, for which the threshold was set at doses lower than the maximum approved dose (6 mg per day for risperidone; 600 mg per day for clozapine) based on expert opinion regarding doses normally used in clinical practice.

With respect to combination therapy with clozapine and another antipsychotic agent (11 studies), the majority of outcomes showed no significant differences in comparison with clozapine monotherapy; however, clozapine combination therapy was slightly better on CGI-Improvement. With respect to harms, total cholesterol and LDL were improved with combination therapy compared with monotherapy; however, more patients had serious adverse events with

combination treatment. While not pooled, due to high heterogeneity, three of five trials reporting prolactin levels found statistically lower levels with clozapine monotherapy, and although not statistically significant, more patients withdrew due to adverse events or suffered from akathisia with clozapine-based combination therapy compared with monotherapy.
The efficacy of non-clozapine AAP combination therapy did not differ significantly from non-clozapine AAP monotherapy; however, only one RCT met inclusion criteria. Differences in harms were seen for prolactin levels and the rate of serious adverse events, both of which were lower with combination therapy.

With the exception of GAF scores, which showed less improvement in the high-dose AAP group, no significant differences in efficacy were found between high-dose non-clozapine AAP treatment and standard-dose clozapine. From the standpoint of harms, more patients experienced EPS and elevated prolactin in high-dose non-clozapine AAP treatment than in standard-dose clozapine treatment. However, fewer patients had Parkinsonism on high-dose AAP treatment compared with standard-dose clozapine, and the rate of withdrawals due to adverse events was also lower in the high-dose AAP group. The discrepancy between incidence of EPS and Parkinsonism with high-dose AAPs relative to clozapine may be due to chance — there was no trial that reported on both outcomes — or due to the higher mean or median doses of AAPs used in the trials reporting EPS (risperidone at 9 mg per day,[60] olanzapine at 23.4 mg per day,[70] and clozapine at 332 mg per day[70] or 600[60] mg per day) versus those reporting Parkinsonism (risperidone at 6.4 mg per day,[66] olanzapine at 20.5 mg per day,[53] and clozapine at 291 mg per day[66] or 303[53] mg per day).

Studies outside the scope of this review indicate that clozapine is more efficacious compared with standard doses of other AAPs in treatment-resistant schizophrenia.[70,105-107] Although there were no statistically significant differences in efficacy between high doses of non-clozapine AAPs and clozapine in the present review, the evidence was of insufficient quality to conclude that these strategies are equivalent. Further studies of higher quality are needed to more definitively assess the comparative efficacy and safety of high doses of non-clozapine AAPs versus clozapine.

When high-dose non-clozapine AAPs were compared with standard-dose non-clozapine APDs, meta-analyses detected no significant differences, although PANSS-total and PANSS-positive scores were statistically significantly improved in a single trial with high-dose risperidone compared with haloperidol.[68]

Overall, the limited evidence available does not support a clinically significant benefit of combination or high-dose AAP treatment strategies in the treatment of schizophrenia. This includes combinations of clozapine and another APD compared with clozapine monotherapy. Although statistical significance was shown for some outcomes as highlighted above, these results should be interpreted with caution, given the uncertain clinical significance of these differences (see Appendix 3 for information on minimal important differences), and the inconsistency in effects across studies and between similar outcomes. There were also few statistically significant differences in harms outcomes, including metabolic parameters. However, it should be noted that statistical power was likely limited, particularly for rarer outcomes such as SAEs and agranulocytosis. Therefore, the available RCT evidence does not provide conclusive evidence to support the safety of combination and high-dose treatment strategies. Observational evidence identified in the accompanying safety review (see Appendix 17) was similarly inconclusive.

Schizophrenia is now conceptualized as a disorder of multiple symptom domains (e.g., positive, negative, cognitive),[108] and the question arises as to how high-dose and combination treatments affect the other features, such as cognitive function. Newer antipsychotics individually have laid claim to improvement in negative and cognitive symptoms, although the magnitude of these changes and implications for clinical benefit have been challenged.[109-111] In addressing these other domains, it is also important to recognize that there may be multiple subdomains for each. In the case of cognition, for example, the recent National Institute of Mental Health MATRICS (Mental Health Measurement and Treatment to Improve Cognition in Schizophrenia) initiative[79,80] has identified seven such areas: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reason and problem-solving, and social cognition.

The currently available clinical evidence fails to substantiate a positive treatment effect for either combination or high-dose AAP strategies in terms of cognition. While individual studies reported significant results, collectively there was no consistent effect in terms of cognition or its subdomains (see Appendix 16). Further, previous findings suggest that a worsening in scores can also occur in the face of such strategies. This is perhaps not surprising, given data linking antipsychotics (typical and atypical) dose or plasma levels to cognitive impairment.[112,113]

The main research gaps identified in the current systematic review include:

- A paucity of studies in pediatric or adolescent populations, and in subpopulations likely to experience greater benefits or greater risk of harm when using combination or high-dose AAP strategies
- Lack of sufficient data on mortality, hospitalizations, relapse rates, suicidality, health-related quality of life, level of function, and long-term adverse effects of combination or high-dose antipsychotic use
- Lack of studies comparing non–clozapine-based AAP combination therapies with clozapine monotherapy, and studies comparing high and standard doses of the same non-clozapine AAP, and studies on long-acting antipsychotic injections, either as part of a combination or high-dose strategy.

## 6.2 Strengths and Weaknesses of Review

### 6.2.1 Strengths

This systematic review used a transparent methodology that was outlined in a protocol specified a priori. A comprehensive list of outcomes was established a priori to assess efficacy and harms, and a large number of subgroup and sensitivity analyses were carried out to explore heterogeneity. In most cases, these analyses demonstrated that the reference case results were robust.

Compared with previously conducted systematic reviews on APD combination therapy[20-24,29] and AAP high dose,[31] the current review is more comprehensive in terms of interventions and outcomes included. This report focuses on patients who are inadequately controlled on standard-dose AAP monotherapy instead of the general population of patients with schizophrenia. Patients who are inadequately controlled are the most likely population to receive combination or high-dose therapy in clinical practice. In addition, this report includes evidence from more recently published studies.

### 6.2.2 Weaknesses

The results and strength of the conclusions presented in this review are limited by the available clinical evidence. Few of the included studies were methodologically robust and all were shorter

than one year in duration. The criteria for defining inadequate control were not always reported, and varied across included studies. Furthermore, in some studies, APD treatment history was not reported and not all studies applied a run-in period to standardize baseline treatments. Outcome definitions also varied across trials (e.g., definition of treatment response, cognitive measures). Such variability in the characteristics of the included studies likely contributed to the substantial degree of heterogeneity seen in some meta-analyses.

There was relatively little evidence for clinically relevant outcomes (e.g., mortality, hospitalizations, quality of life); surrogates such as PANSS and CGI were the primary efficacy outcomes reported in the majority of included RCTs. However, the relationship between the change in PANSS score and long-term clinical outcomes has not been well established.[114] Similar to previous reviews,[19-29,31] a general lack of consistency in the definition and reporting of serious adverse events was also found. Furthermore, event rates for many harm outcomes (such as adverse events) were low, limiting the power to detect important differences in safety between treatment strategies. Longer, high-quality studies are required to determine if high-dose or combination strategies are more or less efficacious or harmful than standard therapies with respect to clinically relevant endpoints such as hospitalizations, quality of life, and functional outcome.

For many studies included in the review, estimation of variance was difficult due to lack of reporting. As a result, these values were calculated from available evidence within the study using estimated correlation values.

Doses of APDs used in the included trials varied and were often poorly reported. For example, clozapine doses varied considerably between studies (mean, median, or mean modal dose range: 291 mg per day[66] to 600 mg per day[60]), and not reported in two abstracts.[74,75] However, post hoc sensitivity analyses, performed for affected comparisons by removing trials with clozapine < 350 mg per day, did not have a significant impact on the results.

In most trials, patient compliance with the trial protocol was not reported; this may have led to bias if compliance was different between treatment arms.
There was also inconsistency regarding the type of primary analysis used in the trials, with nine trials reporting ITT analyses and the remaining reporting non-ITT analyses (e.g., per-protocol analysis). Per-protocol analyses may overestimate the effectiveness of high-dose or combination strategies.

Trials published in languages other than English or French were excluded from this review; hence, articles of potential relevance may have been overlooked as a result of this language restriction. However, a number of studies have suggested that the exclusion of non-English trials has minimal impact on the results of systematic reviews and meta-analyses.[115-118]

## 6.3 Generalizability of Findings

Overall, our findings are consistent with those from NICE[7] and other previously published systematic reviews and meta-analyses that compared clozapine combination therapy with clozapine monotherapy[19-29] or high-dose AAP therapy compared with standard-dose AAP or TAP,[31] although considerable differences exist between this review and previously conducted reviews in terms of population, intervention/comparators, outcomes of interest, definitions of outcomes, and methods used in the meta-analyses.

Similar to the conclusions of the recent NICE[7] review, the results of this review show that, in comparison with standard therapies, there is no evidence of improved clinical benefit using treatment with high-dose or combination AAP therapies in patients with schizophrenia who are inadequately controlled on antipsychotic monotherapy. Furthermore, also consistent with other systematic reviews on high-dose[31] and combination strategies,[19-29] the evidence regarding harms was inconclusive.

There were a number of issues that may reduce the generalizability of the findings of this review to the Canadian population of patients with schizophrenia. Patients in clinical studies are more likely to have higher compliance rates and greater access to care than the general population. Some of the included studies were conducted in countries where clinical management of schizophrenia may differ substantially from Canada (e.g., Turkey, Korea). Furthermore, several studies included agents that are not available in Canada, although sensitivity analyses removing these drugs showed similar results to those in the reference case analysis. Finally, the population of interest for this systematic review was patients inadequately controlled with standard-dose antipsychotics. However, the available RCTs included patients with various treatment histories and, in most cases, treatment history was not reported. Furthermore, in some cases, definitions of inadequate control were either not reported or were inconsistent across studies. Hence, the extent to which trial populations were reflective of patients in Canada treated with high-dose or combination strategies is uncertain. It is noteworthy, however, that studies were consistent in reporting a lack of significant differences in efficacy between high-dose or combination strategies and standard-dose APDs despite the heterogeneity in trial populations. It is therefore likely that the results of this review are largely applicable to patients in Canada with schizophrenia for whom these treatment strategies are considered.

# 7 CONCLUSIONS

High-dose and combination strategies involving AAPs are frequently used in clinical practice for patients with schizophrenia who are inadequately controlled with one or more AAPs used at standard doses. In this systematic review and meta-analysis to assess the relative safety and efficacy of combination therapy and high-dose atypical antipsychotic therapy in patients with schizophrenia inadequately controlled on standard-dose antipsychotics, no clinically significant improvements were found favouring combination or high-dose AAP treatment strategies when compared with standard-dose monotherapy. In terms of safety, no clinically significant differences were evident between combination or high-dose therapy in comparison with standard-dose monotherapy, with the exception of clozapine combination therapy where patients experienced more serious adverse events compared with clozapine monotherapy. However, the safety evidence was considered inconclusive, due to the sparsity of data for key harms-related outcomes.

Limitations of this systematic review include paucity and low quality of available evidence; heterogeneity in reported outcomes; lack of data on many clinically important outcomes; short duration of trials; and inadequate study power, particularly for safety outcomes.

In order to determine with more certainty whether combination or high-dose treatment strategies have clinical value in treatment-resistant patients with schizophrenia, longer-term studies of sufficient methodological quality and sample size are required. Given its role as standard of care for treatment-resistant patients, further comparative trials with clozapine may be of particular utility in clarifying the optimal treatment algorithm for patients with schizophrenia.

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# APPENDIX 1: LITERATURE SEARCH STRATEGY

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| .sh | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| exp | Explode a subject heading |
| * | Before a term, indicates that the marked subject heading is a primary topic;<br>or, immediately after a word, a truncation symbol (wildcard) to retrieve plurals or variant word endings |
| adj# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .pt | Publication type |
| .rn | CAS registry number |
| .nm | Name of substance word |
| cctr | Cochrane Central Register of Controlled Trials |
| .po | Population group |
| .la | Language |
| .lg | Language |
| .mp | Mapped word |
| .jw | Journal word |
| .md | Methodology |
| .yr | Year |

Search Strategy for Randomized Controlled Trials and Controlled Clinical Trials

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Cochrane Central Register of Controlled Trials <2nd Quarter 2010>;<br>EMBASE <1980 to 2010 Week 23>;<br>Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 15, 2010>;<br>Ovid MEDLINE(R) <1950 to June Week 1 2010>;<br>PsycINFO <1967 to June Week 2 2010><br>**Note**: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | June 16, 2010 |
| Alerts: | Monthly until publication of report |
| Study Types: | Randomized controlled trials; Controlled clinical trials |
| Limits: | Publication dates – no limit<br>Human population<br>English or French language |

**Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process, Cochrane Central, PsycINFO**

| Line # | Strategy |
|---|---|
| 1 | exp schizophrenia/ or schizophrenia.hw. |
| 2 | (schizophreni* or schizoaffect* or schizo affect* or hebephreni* or schizophreniform or dementia praecox or dementia precox or shared paranoid disorder* or (delusional adj2 disorder*) or (brief psychotic adj2 disorder*) or first psychotic episode* or first episode psychos*).ti,ab. |
| 3 | or/1-2 |
| 4 | risperidone/ |
| 5 | clozapine/ |
| 6 | aripiprazole*.rn. |
| 7 | olanzapine*.rn. |
| 8 | quetiapine*.rn. |
| 9 | 9-hydroxy-risperidone*.rn. |
| 10 | ziprasidone*.rn. |
| 11 | asenapine*.rn. |
| 12 | (risperidone* or clozapine* or aripiprazole* or olanzapine* or quetiapine* or 9-hydroxy-risperidone* or paliperidone* or ziprasidone* or ziprazidone* or asenapine*).ti,ab,nm,hw. |
| 13 | (risperdal* or risperidal* or belivon* or rispolin* or risperin* or rispolept* or sequinan* or zyprexa* or olansek* or seroquel* or clozaril* or clorazil* or fazaclo* or iprox* or leponex* or abilify* or abilitat* or invega* or geodon* or zeldox* or saphris*).ti,ab. |
| 14 | ((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 antipsychotic*).ti,ab. |
| 15 | ((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 anti-psychotic*).ti,ab. |
| 16 | ((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 neuroleptic*).ti,ab. |
| 17 | (106266-06-2 or 132539-06-1 or 111974-69-7 or 129722-12-9 or 5786-21-0 or 144598-75-4 or 146939-27-7 or 85650-56-2).rn. |
| 18 | or/4-17 |
| 19 | 3 and 18 |
| 20 | drug combinations/ |
| 21 | exp drug therapy, combination/ |
| 22 | polypharmacy/ |
| 23 | (augmentation or add-on or adjunctive or adjunct or adjuvant or added or polypharmac* or polytherap* or combination* or combined or combining or co-therap* or cotherap* or co-administration or coadministration or (dual adj2 therap*) or concomitant or concurrent or monotherap* or monotreatment or mono-therap* or mono-treatment* or mono-administration).ti,ab. |
| 24 | or/20-23 |
| 25 | dose-response relationship, drug/ |

26 drug dosage calculations/

27 no-observed-adverse-effect level/

28 maximum tolerated dose/

29 drug dosages/

30 (dose or doses or dosage* or dosing).ti,ab.

31 or/25-30

32 24 or 31

33 19 and 32

34 (Randomized Controlled Trial or Controlled Clinical Trial).pt.

35 Randomized Controlled Trial/

36 Randomized Controlled Trials as Topic/

37 Controlled Clinical Trial/

38 Controlled Clinical Trials as Topic/

39 Randomization/

40 Random Allocation/

41 Double-Blind Method/

42 Double Blind Procedure/

43 Double-Blind Studies/

44 Single-Blind Method/

45 Single Blind Procedure/

46 Single-Blind Studies/

47 Placebos/

48 Placebo/

49 Control Groups/

50 Control Group/

51 (random* or sham or placebo*).ti,ab,hw.

52 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

53 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

54 (control* adj3 (study or studies or trial*)).ti,ab.

55 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.

56 "allocated to".ti,ab,hw.

57 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.

| | |
|---|---|
| 58 | or/34-57 |
| 59 | 33 and 58 |
| 60 | 33 use cctr |
| 61 | 59 or 60 |
| 62 | exp animals/ |
| 63 | exp animal experimentation/ |
| 64 | exp models animal/ |
| 65 | exp animal experiment/ |
| 66 | nonhuman/ |
| 67 | exp vertebrate/ |
| 68 | animal.po. |
| 69 | or/62-68 |
| 70 | exp humans/ |
| 71 | exp human experiment/ |
| 72 | human.po. |
| 73 | or/70-72 |
| 74 | 69 not 73 |
| 75 | 61 not 74 |
| 76 | limit 75 to english language [Limit not valid in CCTR; records were retained] |
| 77 | 75 and french.la,lg. |
| 78 | 76 or 77 |

**Embase**

| Line # | Strategy |
|---|---|
| 1 | exp *schizophrenia/ |
| 2 | (schizophreni* or schizoaffect* or schizo affect* or hebephreni* or schizophreniform or dementia praecox or dementia precox or shared paranoid disorder* or (delusional adj2 disorder*) or (brief psychotic adj2 disorder*) or first psychotic episode* or first episode psychos*).ti,ab. |
| 3 | or/1-2 |
| 4 | *risperidone/ or *clozapine/ or *aripiprazole/ or *olanzapine/ or *quetiapine/ or *paliperidone/ or *ziprasidone/ or *asenapine/ |
| 5 | (risperidone* or clozapine* or aripiprazole* or olanzapine* or quetiapine* or 9-hydroxy-risperidone* or paliperidone* or ziprasidone* or ziprazidone* or asenapine*).ti,ab. |
| 6 | (risperdal* or risperidal* or belivon* or rispolin* or risperin* or rispolept* or sequinan* or zyprexa* or olansek* or seroquel* or clozaril* or clorazil* or fazaclo* or iprox* or leponex* or abilify* or abilitat* |

| | |
|---|---|
| | or invega* or geodon* or zeldox* or saphris*).ti,ab. |
| 7 | ((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 antipsychotic*).ti,ab. |
| 8 | ((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 anti-psychotic*).ti,ab. |
| 9 | ((atypical or new generation or second generation or 2nd generation or next generation or novel) adj2 neuroleptic*).ti,ab. |
| 10 | or/4-9 |
| 11 | 3 and 10 |
| 12 | drug combination/ |
| 13 | polypharmacy/ |
| 14 | add-on therapy/ |
| 15 | adjuvant therapy/ |
| 16 | drug mixture/ |
| 17 | monotherapy/ |
| 18 | (augmentation or add-on or adjunctive or adjunct or adjuvant or added or polypharmac* or polytherap* or combination* or combined or combining or co-therap* or cotherap* or co-administration or coadministration or (dual adj2 therap*) or concomitant or concurrent or monotherap* or monotreatment or mono-therap* or mono-treatment* or mono-administration).ti,ab. |
| 19 | or/12-18 |
| 20 | dose response/ |
| 21 | dose calculation/ |
| 22 | maximum permissible dose/ |
| 23 | maximum tolerated dose/ |
| 24 | dosage schedule comparison/ |
| 25 | drug dose comparison/ |
| 26 | drug dose escalation/ |
| 27 | drug dose increase/ |
| 28 | drug dose reduction/ |
| 29 | drug dose regimen/ |
| 30 | drug dose sequence/ |
| 31 | drug dose titration/ |
| 32 | drug megadose/ |
| 33 | maintenance drug dose/ |
| 34 | multiple drug dose/ |
| 35 | optimal drug dose/ |

36 recommended drug dose/

37 (dose or doses or dosage* or dosing).ti,ab.

38 or/20-37

39 19 or 38

40 11 and 39

41 Randomized Controlled Trial/

42 Randomized Controlled Trials as Topic/

43 Controlled Clinical Trial/

44 Controlled Clinical Trials as Topic/

45 Randomization/

46 Random Allocation/

47 Double-Blind Method/

48 Double Blind Procedure/

49 Double-Blind Studies/

50 Single-Blind Method/

51 Single Blind Procedure/

52 Single-Blind Studies/

53 Placebos/

54 Placebo/

55 Control Groups/

56 Control Group/

57 (random* or sham or placebo*).ti,ab,hw.

58 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

59 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

60 (control* adj3 (study or studies or trial*)).ti,ab.

61 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.

62 allocated.ti,ab,hw.

63 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.

64 or/41-63

65 40 and 64

66 exp animals/

67 exp animal experimentation/

68 exp models animal/

69 exp animal experiment/

70 nonhuman/

71 exp vertebrate/

72 or/66-71

73 exp humans/

74 exp human experiment/

75 or/73-74

76 72 not 75

77 65 not 76

78 limit 77 to english language

79 77 and french.la.

80 78 or 79

| OTHER DATABASES | |
|---|---|
| PubMed | Same MeSH and keywords as per MEDLINE search, with appropriate syntax used. Search limited to publisher in the status field. |
| CINAHL | Same keywords used as per MEDLINE search. CINAHL subject headings added. Search limited to clinical trial in publication type field. Syntax adjusted for CINAHL database. |

Search Strategy for Systematic Reviews, Meta-analyses, and Clinical Practice Guidelines

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 16, 2010>; Ovid MEDLINE(R) <1950 to May Week 3 2010> |
| Date of Search: | May 17, 2010 |
| Alerts: | Monthly until publication of report |
| Study Types: | Systematic reviews; meta-analyses; technology assessments; clinical practice guidelines; review articles |
| Limits: | Publication dates: 2004-present. Review articles: 2009-present |

**Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process**

| Line # | Strategy |
|---|---|
| 1 | meta-analysis.pt. |
| 2 | meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/ |
| 3 | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. |
| 4 | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. |
| 5 | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. |
| 6 | (data synthes* or data extraction* or data abstraction*).ti,ab. |
| 7 | (handsearch* or hand search*).ti,ab. |
| 8 | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. |
| 9 | (met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab. |
| 10 | (meta regression* or metaregression* or mega regression*).ti,ab. |
| 11 | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. |
| 12 | (medline or Cochrane or pubmed or medlars).ti,ab,hw. |
| 13 | (cochrane or health technology assessment or evidence report).jw. |
| 14 | (meta-analysis or systematic review).md. |
| 15 | or/1-14 |
| 16 | risperidone/ |
| 17 | clozapine/ |
| 18 | aripiprazole.rn. |
| 19 | olanzapine.rn. |
| 20 | quetiapine.rn. |
| 21 | 9-hydroxy-risperidone.rn. |
| 22 | ziprasidone.rn. |
| 23 | asenapine.rn. |
| 24 | (risperidone or clozapine or aripiprazole or olanzapine or quetiapine or 9-hydroxy-risperidone or paliperidone or ziprasidone or asenapine).ti,ab,nm. |
| 25 | (risperdal or risperidal or belivon or rispolin or risperin or rispolept or sequinan or zyprexa or olansek or seroquel or clozaril or clorazil or fazaclo or iprox or leponex or abilify or abilitat or invega or geodon or zeldox or saphris).ti,ab. |
| 26 | ((atypical or new generation or second generation or 2nd generation or novel) adj2 antipsychotic*).ti,ab. |
| 27 | ((atypical or new generation or second generation or 2nd generation or novel) adj2 anti- |

| | |
|---|---|
| | psychotic*).ti,ab. |
| 28 | ((atypical or new generation or second generation or 2nd generation or novel) adj2 neuroleptic*).ti,ab. |
| 29 | (106266-06-2 or 132539-06-1 or 111974-69-7 or 129722-12-9 or 5786-21-0 or 144598-75-4 or 146939-27-7 or 85650-56-2).rn. |
| 30 | or/16-29 |
| 31 | drug combinations/ |
| 32 | exp drug therapy, combination/ |
| 33 | polypharmacy/ |
| 34 | (augmentation or add-on or adjunctive or adjunct or adjuvant or added or polypharmac* or polytherap* or combination* or combined or combining or co-therap* or cotherap* or co-administration or coadministration or (dual adj2 therap*) or monotherap* or monotreatment or mono-administration).ti,ab. |
| 35 | or/31-34 |
| 36 | dose-response relationship, drug/ |
| 37 | drug dosage calculations/ |
| 38 | no-observed-adverse-effect level/ |
| 39 | maximum tolerated dose/ |
| 40 | (dose or doses or dosage* or dosing).ti,ab. |
| 41 | or/36-40 |
| 42 | 35 or 41 |
| 43 | (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. |
| 44 | (guideline* or standards or consensus* or recommendat*).ti. |
| 45 | (practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti. |
| 46 | (care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard or standards)).ti. |
| 47 | ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti. |
| 48 | (algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti. |
| 49 | (algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti. |
| 50 | or/43-49 |
| 51 | exp schizophrenia/ |
| 52 | (schizophreni* or schizoaffect* or schizo affect* or hebephreni* or schizophreniform or dementia praecox or dementia precox or shared paranoid disorder* or (delusional adj2 disorder*) or (brief psychotic adj2 disorder*) or first psychotic episode*).ti,ab. |
| 53 | or/51-52 |

54 53 and 30 and 42 and 15

55 limit 54 to yr="2004 -Current"

56 50 and 53 and 30

57 limit 56 to yr="2004 -Current"

58 55 or 57

**Additional Schizophrenia Guidelines That Don't Specifically Mention Atypical Antipsychotic Drug names**

59 50 and 53

60 59 not 56

61 limit 60 to yr="2004 -Current"

**Review Articles**

62 53 and 30 and 42

63 review.pt,ti

64 62 and 63

65 limit 64 to yr="2009 -Current"

## Grey Literature and Handsearches

| | |
|---|---|
| Dates for Search: | June 2010 |
| Keywords: | Atypical antipsychotics, second generation antipsychotics, novel antipsychotics, schizophrenia |

This section lists the main agencies, organizations, and websites searched; it is not a complete list.

**Health Technology Assessment Agencies**

Institut national d'excellence en santé et en services sociaux (INESSS) [succeeded AETMIS]
http://www.inesss.qc.ca/

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca

Health Technology Assessment International (HTAi)
http://www.htai.org

International Network of Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org

NHS Health Technology Assessment/National Coordinating Centre for Health Technology Assessment (NCCHTA), Department of Health, R&D Division
http://www.ncchta.org

NHS National Institute for Health and Clinical Excellence (NICE)
http://www.nice.org.uk

University of York NHS Centre for Reviews and Dissemination (NHS CRD)
http://www.york.ac.uk/inst/crd

The Wessex Institute for Health Research and Development, Succinct and Timely Evaluated Evidence Review (STEER)
http://www.wihrd.soton.ac.uk/

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/

US Department of Veterans Affairs Research & Development, general publications
http://www.research.va.gov/resources/pubs/default.cfm

VA Technology Assessment Program (VATAP)
http://www.va.gov/vatap/

ECRI
http://www.ecri.org/

**Search Engines**

Google
http://www.google.ca/

# APPENDIX 2: SUMMARY OF OUTCOMES AS RANKED BY MEMBERS OF COMPUS EXPERT REVIEW COMMITTEE

| Outcomes | Median Ranking Score* |
|---|---|
| Efficacy | |
| PANSS — total | 7 |
| PANSS — positive | 6 |
| PANSS — negative | 5 |
| BPRS | 7 |
| CGI-I | 7 |
| CGI-S | 6 |
| Response rate | 6 |
| Relapse rate | 7 |
| Clinical remission | 7 |
| Functional capacity | 7 |
| Quality of life | 7 |
| Persistence with therapy | 7 |
| Harms | |
| BARS | 7 |
| AIMS | 6 |
| SAS | 7 |
| EPS | 7 |
| Cognitive impairment | 8 |
| All-cause mortality | 8 |
| Suicidality | 7 |
| Cardiovascular events | 7 |
| Incident diabetes | 6 |
| Prolactinemia | 4 |
| Hemoglobin A1C | 4 |
| Fasting plasma glucose | 4 |
| Lipid profile (total cholesterol, LDL, HDL, triglycerides) | 5 |
| Agranulocytosis | 8 |
| Serious/severe adverse events | 8 |
| Withdrawals due to adverse events | 7 |
| Hospitalization | 8 |

AIMS = Abnormal Involuntary Movement scale; BARS = Barnes Akathisia Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression — Improvement scale; CGI-S = Clinical Global Impression — Severity scale; CI = confidence interval; DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale; EPS = extrapyramidal symptoms; GAF = Global Assessment of Functioning; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N/A = not applicable; PANSS = Positive and Negative Symptom Scale; SAS = Simpson-Angus Scale.

*Scores of 7–9 represent critical outcomes, 4–6 represent important outcomes, and 1–3 represent unimportant outcomes.

# APPENDIX 3: VALIDITY OF PSYCHIATRIC SYMPTOM SCALES AND CLINICAL IMPLICATIONS

**Positive and Negative Syndrome Scale (PANSS):** The PANSS was developed as a 30-item rating scale, which adapted 18 items from the Brief Psychiatric Rating Scale (BPRS) and 12 items from the Psychopathology Rating Schedule (PRS).[119] The PANSS requires a 30 to 40 minute patient interview to gather information on which to assess the patient with regard to the presence and severity of psychopathology in the previous week. The PANSS instrument provides a complete definition of each item as well as detailed anchoring criteria for each of seven rating points: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate–severe, 6 = severe, 7 = extreme. In the 30-item scale, seven items related to positive symptoms, seven items to negative symptoms, and 16 items to general psychopathology (as shown below). Finally, a composite scale may be derived by subtracting the negative score from the positive score. The 30 items of the PANSS are presented below:[120]

**Positive Scale**
P1. Delusions
P2. Conceptual disorganization
P3. Hallucinatory behaviour
P4. Excitement
P5. Grandiosity
P6. Suspiciousness
P7. Hostility
**Negative Scale**
N1. Blunted affect
N2. Emotional withdrawal
N3. Poor rapport
N4. Passive/apathetic social withdrawal
NS. Difficulty in abstract thinking
N6. Lack of spontaneity and flow of conversation
N7. Stereotyped thinking
**General Psychopathology Scale**
G1. Somatic concern
G2. Anxiety
G3. Guilt feelings
G4. Tension
G5. Mannerisms & posturing
G6. Depression
G7. Motor retardation
G8. Uncooperativeness
G9. Unusual thought content
G10**.** Disorientation
G11**.** Poor attention
G12. Lack of judgment and insight
G13. Disturbance of volition
G14. Poor impulse control
G15. Preoccupation
G16. Active social avoidance

Kay et al. reported on psychometric testing of the PANSS in 101 in-patients with schizophrenia.[119] Scores on all subscales were reported to exhibit a normal distribution, suggesting suitability for parametric statistical analysis. Further, the range of scores was less than the potential range, suggesting the lack of a ceiling effect. Internal consistency was demonstrated for the positive ($\alpha = 0.73$), negative ($\alpha = 0.83$), and general psychopathology ($\alpha = 0.79$) subscales. Test-retest reliability was assessed three to six months later on a cohort of 15 patients who remained hospitalized; Pearson correlation coefficients were 0.80,

0.68, and 0.60 for the positive, negative, and general psychopathology subscales, respectively.[11] Peralta and Cuesta reported on the inter-rater reliability of the PANSS from a sample of 100 consecutively admitted patients with schizophrenia.[121] Positive and negative scales showed good inter-rater reliability: interclass correlation coefficients (ICC) of 0.72 and 0.80, respectively. Inter-rater reliability was moderate for the general psychopathology scale; ICC = 0.56.

More recently, a number of investigators have conducted principal components analysis to expand the identification of discrete dimensions of schizophrenia beyond the focus on positive and negative symptoms. A number of similar five-factor models, including most or all of the original PANSS items, have been proposed and tested for reliability and validity.[122-126] One such model was proposed by Marder et al. and categorizes all original PANSS items into five dimensions: positive symptoms (eight items), negative symptoms (seven items), disorganized thought (seven items), uncontrolled hostility/excitement (four items), and anxiety/depression (four items).[126]

It is unclear what degree of improvement in the PANSS total or subscale scores is clinically important. The relationship between change in PANSS score and long-term clinical outcomes has not been clearly identified;[114] however, a 20% reduction of PANSS has been used as the criterion of response to antipsychotic treatment in many clinical trials.[36,39,42] In a comparison of PANSS to the Clinical Global Impression (CGI) tool, it is suggested that an absolute reduction of 15 in the total PANSS score corresponds to "minimally improved" on the CGI—Improvement (CGI-I) scale, and a reduction of the CGI—Severity (CGI-S) score by one severity step.[127] A reduction of 33 in the total PANSS score corresponds to "much improved" on the CGI-I scale. The above estimates are sensitive to baseline severity of illness to the extent that participants with a lower baseline severity of illness required smaller reductions in the PANSS to produce a particular improvement in the CGI. For this reason, it has been suggested that change in PANSS score has limited usefulness as a primary outcome, due to variability in baseline symptom intensity.[128,129] Instead, a standardized remission criterion that may be suitable for use in clinical practice and clinical trials has been proposed. Specifically, a score of ≤ 3 on all eight PANSS items (P1, P2, P3, N1, N4, N6, G5, and G9) for a period of at least six months is considered to represent remission of disease.[128,129]

**Brief Psychiatric Rating Scale (BPRS):** Consists of 24 symptom constructs, each rated on a seven-point scale of severity ranging from "not present" to "extremely severe" (1 = not present; 2 = very mild; 3 = mild; 4 = moderate; 5 = moderately severe; 6 = severe; 7 = extremely severe). Research suggests that a reduction of at least 10 points correlates with "minimally improved" on the CGI-I and to a change in CGI-S score of one severity step.[127] Similar to PANSS, the clinical implications of BPRS change are not well established, although 20% reduction of BPRS was used as a criterion of response to antipsychotic treatment in many clinical trials.[46,51,65]

**Clinical Global Impressions (CGI):** The CGI scale is a three-item scale used to assess overall severity and response to treatment of mental disorders. It is not specific to schizophrenia, although efforts to adapt the scale specifically to this disorder have been undertaken.[130] The three scale items include severity of illness (CGI-S), overall improvement (CGI-I), and an efficacy index. **CGI-S** is a seven-point scale that indicates how mentally ill the patient is at a given time: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.[131] **CGI-I** is a seven-point scale that indicates symptom improvement after the treatment: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change from baseline; 5 = minimally worse; 6 = much worse; 7 = very much worse).[131] CGI-I is only measured after treatment. A CGI-I score of 1 or 2 was used as a response criterion in some trials.[36,40] The **efficacy index** incorporates the clinician's assessment of therapeutic effect in relation to adverse events. The difficulty of combining the two concepts of efficacy and adverse events has led to criticism of this last item.[130] However, there is no total score for the CGI; rather, scores on the individual items are considered separately.

As the CGI can be administered quickly, it is well suited to clinical settings; however, there is little information regarding its reliability or validity. Rabinowitz et al. sought to validate the CGI-S via a comparison of PANSS and CGI-S scores from seven trials of risperidone in schizophrenia.[132] CGI-S scores from the pooled trials corresponded to the following mean PANSS scores: 1 (normal) = PANSS

55.5; 2 (borderline ill) = PANSS 67.0; 3 (mildly ill) = PANSS 79.6; 4 (moderately ill) = PANSS 92.4; and 5 (markedly ill) = PANSS 99.7. Predefined measures of clinical improvement were a 20% reduction in the PANSS score and a 1-point decrease on the CGI-S. The sensitivities and specificities for the CGI-S to detect this level of improvement in the seven trials ranged from 64.5% to 89.6% and 65.7% to 82.8%, respectively. From this assessment, it appears that the CGI-S and PANSS are correlated and exhibit substantial agreement in detecting change.

**Barnes Akathisia Rating Scale (BARS):** The BARS is the most commonly used scale to measure antipsychotic-induced akathisia in clinical trials.[133] The BARS is a four-item scale that scores patients' akathisia based on (i) brief observation by the clinician (ranked 0 to 3); (ii) patient report of awareness of restlessness (ranked 0 to 3); (iii) patient report of distress related to restlessness (ranked 0 to 3), which produces (iv) a global clinical assessment of akathisia.[134] The global clinical assessment contains five well-defined severity categories that are considered clinically relevant: 0 = absent; 1 = questionable; 2 = mild; 3 = moderate; 4 = marked; 5 = severe.[133] Inter-rater reliability for all four items, based on duplicate rating of 42 chronic in-patients and measured by Cohen's kappa, were observation (0.74), awareness (0.83), distress (0.90), and global clinical assessment (0.96).[134] The BARS has been reported to correlate only weakly with motor activity measured by actometry, potentially due to the fact that actometry measures only actual movement, while the BARS also measures the subjective experience of awareness and distress.[135]

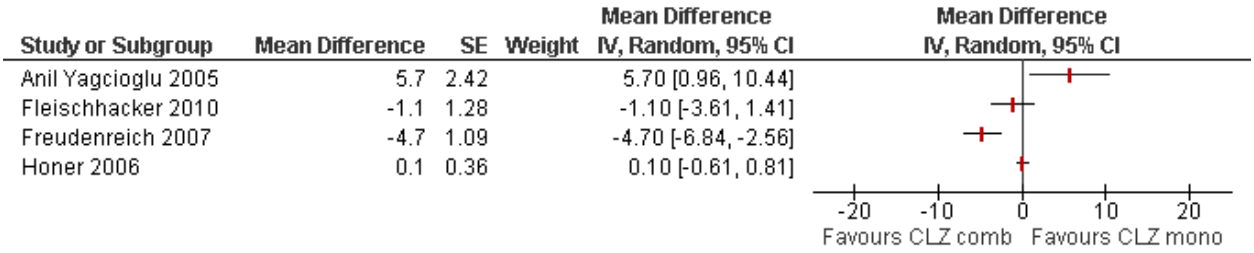
**Abnormal Involuntary Movement Scale (AIMS):** The AIMS is a 12-item scale for assessing dyskinesias completed by the clinician or researcher. The first seven items pertain to abnormal movements in three specific anatomical sites: facial and oral movements (four items), extremity movements (two items), and trunk movements (one item).[136] The remaining items are global assessments (three items, including global severity, incapacitation, and patient awareness), and two items specific to dentition. Except for the items related to dentition, items are scored on a five-point scale; none (0), normal (1), minimal (2), mild (3), moderate (4), or severe (5). Inter-rater reliability in a sample of 38 outpatients with a history of dyskinesia was reported to be high; Pearson correlation coefficient = 0.87 for all items except those related to dentition.[137] However, inter-rater reliability is reported to be higher among experienced raters.[138] The validity of the AIMS has been established via comparisons to other similar instruments; the Extrapyramidal Symptom Rating Scale (ESRS) and the Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD).[139,140] Gharabawi et al. examined associations between individually related and overall severity scores from the AIMS and ESRS via logistic regression.[139] $R^2$ values ranged from 0.30 (trunk movements) and 0.67 (lips and perioral area); $R^2$ value was 0.56 for global severity. Loonen examined associations between (i) total AIMS scores, (ii) total items excluding global and dental items, and (iii) four facial and oral movement items.[140] Spearman's correlation coefficients between the active global dyskinesia subscale of the SADIMoD and the above AIMS scores were 0.76, 0.82, and 0.83, respectively. It is unclear what would constitute a meaningful change in the AIMS. However, the presence of tardive dyskinesia is accepted based on a rating of mild in two or more anatomical areas, or moderate or greater symptoms in one or more anatomical areas.[139,141,142]

**Simpson-Angus Scale (SAS):** The Simpson-Angus Scale was developed in the 1960s to identify neuroleptic-induced parkinsonism. The scale contains 10 items: one measuring gait, six measuring rigidity, and three measuring glabella tap, tremor, and salivation.[143] Each item is scored on a five-point scale from 0 (complete absence) to 4 (extreme), and a total score is obtained by adding all item scores and dividing by 10 (the total number of items). Scores of up to 0.3 were considered to be within the normal range; however, it has recently been suggested that the upper limit of normal be raised to 0.65.[143] Inter-rater reliability of the SAS between two physicians in a trial of haloperidol containing 14 participants was determined; a correlation coefficient of 0.87 was reported.[144] In this same trial, SAS scores were significantly higher for participants treated with haloperidol compared with placebo, supporting the discriminant validity of the SAS.

# APPENDIX 4: FOREST PLOTS FROM RANDOM EFFECTS META-ANALYSIS (REFERENCE CASE ANALYSES AND SUBGROUPS BY DRUG)

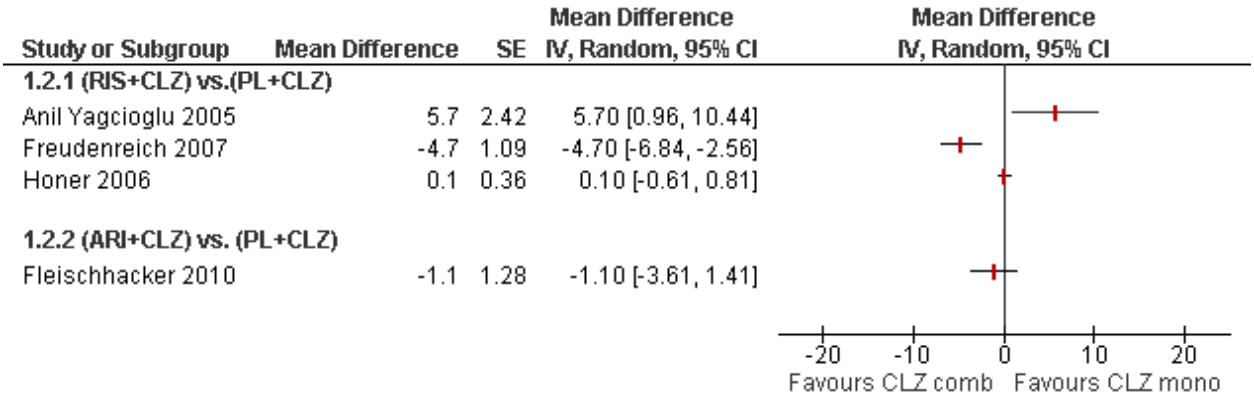
**1. CLZ Combination Therapy versus CLZ Monotherapy (Figures A1.1 – A1.41)**

Figure A1.1: Forest plot for CLZ comb versus CLZ mono: PANSS-T (WMD of changes from baseline (95% CI)) – reference case




*Results not pooled due to high heterogeneity.

Figure A1.2 Forest plot for CLZ comb versus CLZ mono: PANSS-T (WMD of changes from baseline (95% CI)) — subgroup by Drugs*




*Results not pooled due to high heterogeneity.

Figure A1.3: Forest plot for CLZ comb versus CLZ mono: PANSS-P (WMD of changes from baseline (95% CI)) — reference case

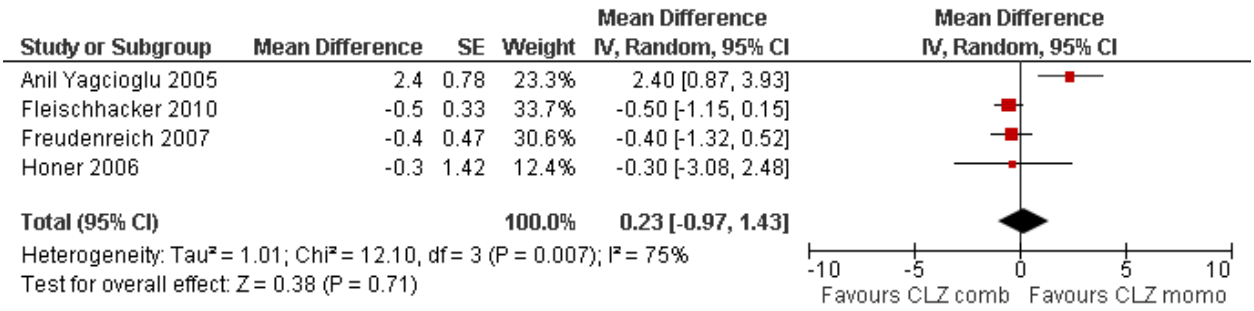
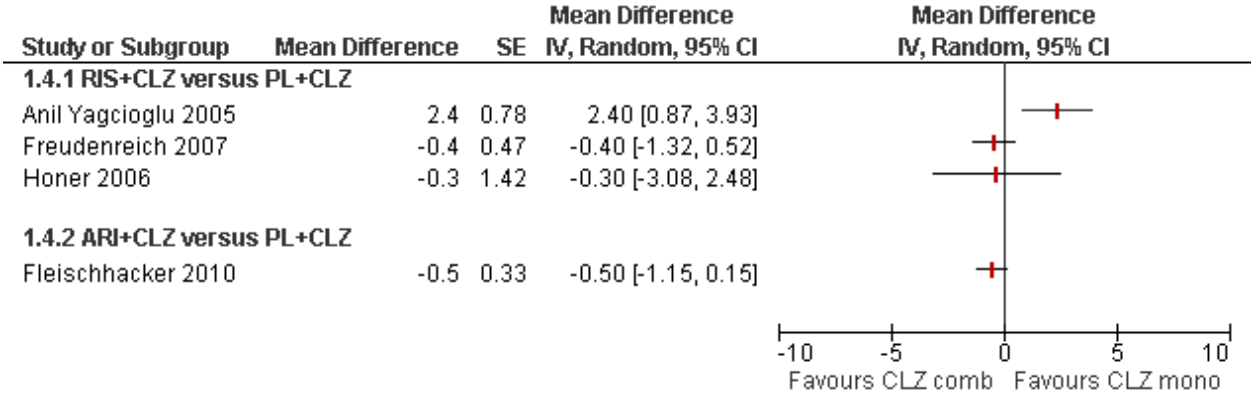



Figure A1.4: Forest plot for CLZ comb versus CLZ mono: PANSS-P (WMD of changes from baseline (95% CI)) — subgroup by drugs*




*Results not pooled due to high heterogeneity.

Figure A1.5: Forest plot for CLZ comb versus CLZ mono: PANSS-N (WMD of changes from baseline (95% CI)) — reference case

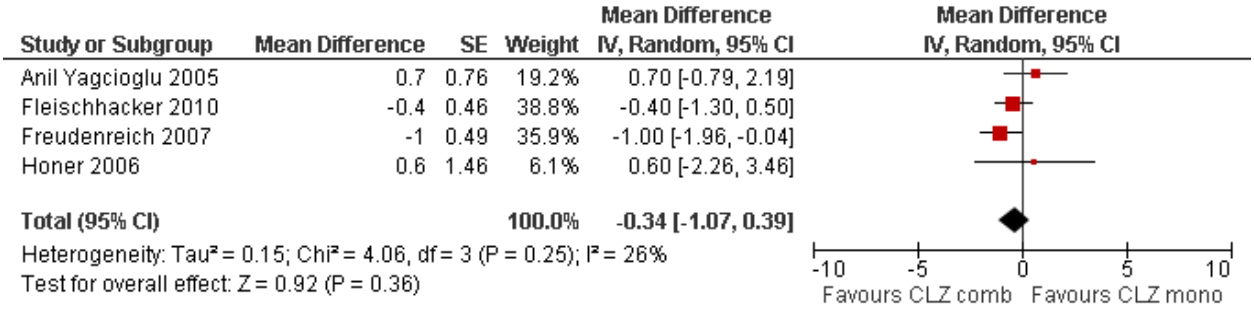


Figure A1.6: Forest plot for CLZ comb versus CLZ mono: PANSS-N (WMD of changes from baseline (95% CI)) — subgroup by drugs

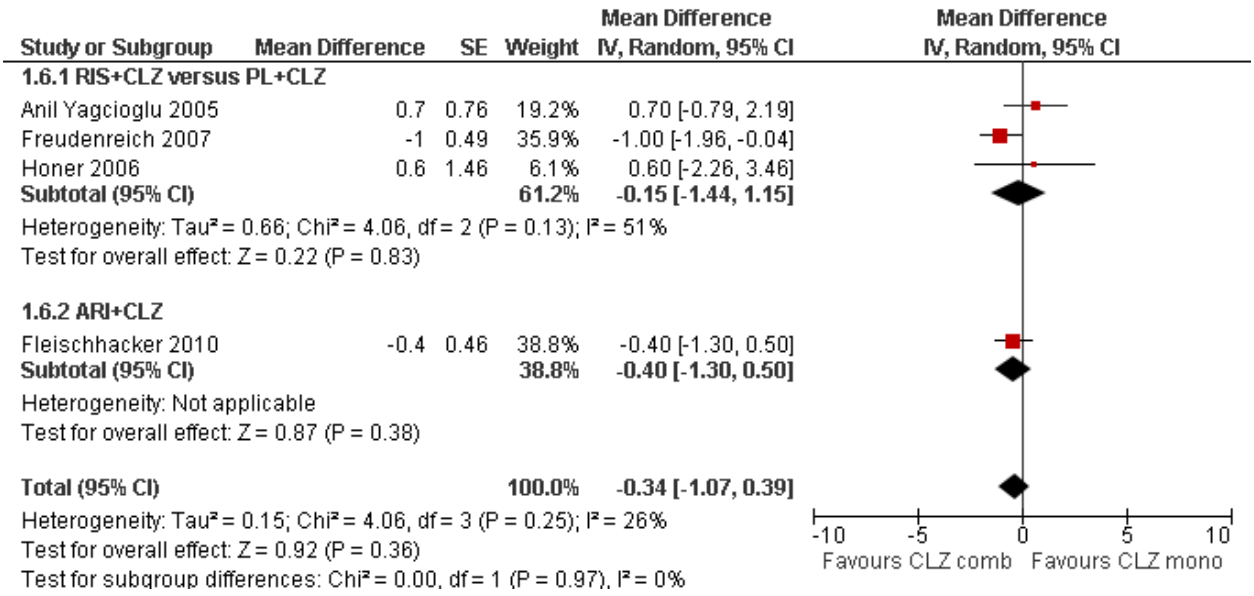



Figure A1.7: Forest plot for CLZ comb versus CLZ mono: BPRS (WMD of changes from baseline (95% CI)) — reference case

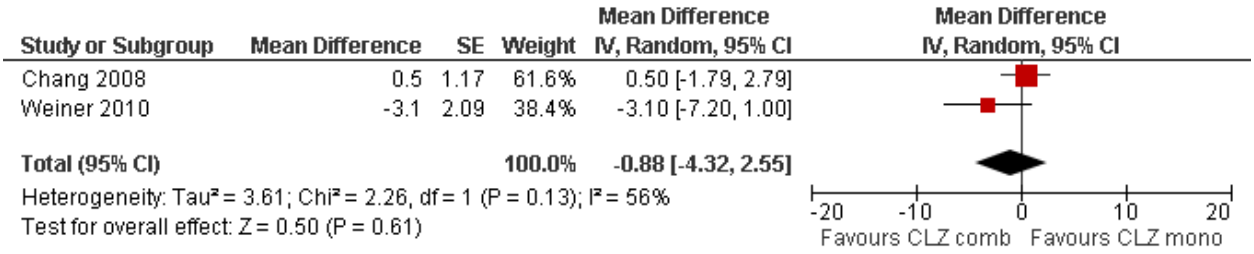


Figure A1.8: Forest plot for CLZ comb versus CLZ mono: BPRS (WMD of changes from baseline (95% CI)) — subgroup by drugs

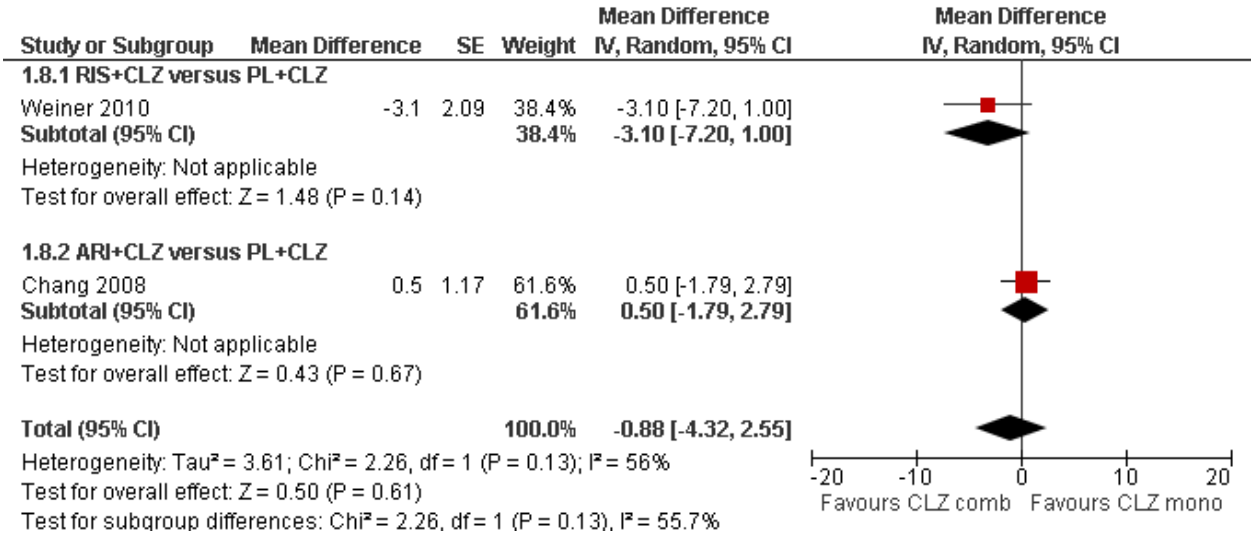



Figure A1.9: Forest plot for CLZ comb versus CLZ mono: CGI-S (WMD of changes from baseline (95% CI)) — Reference case

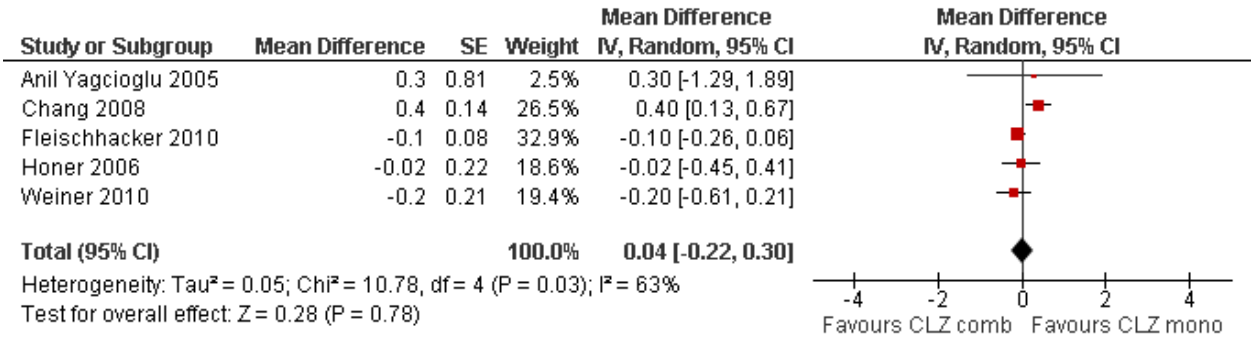
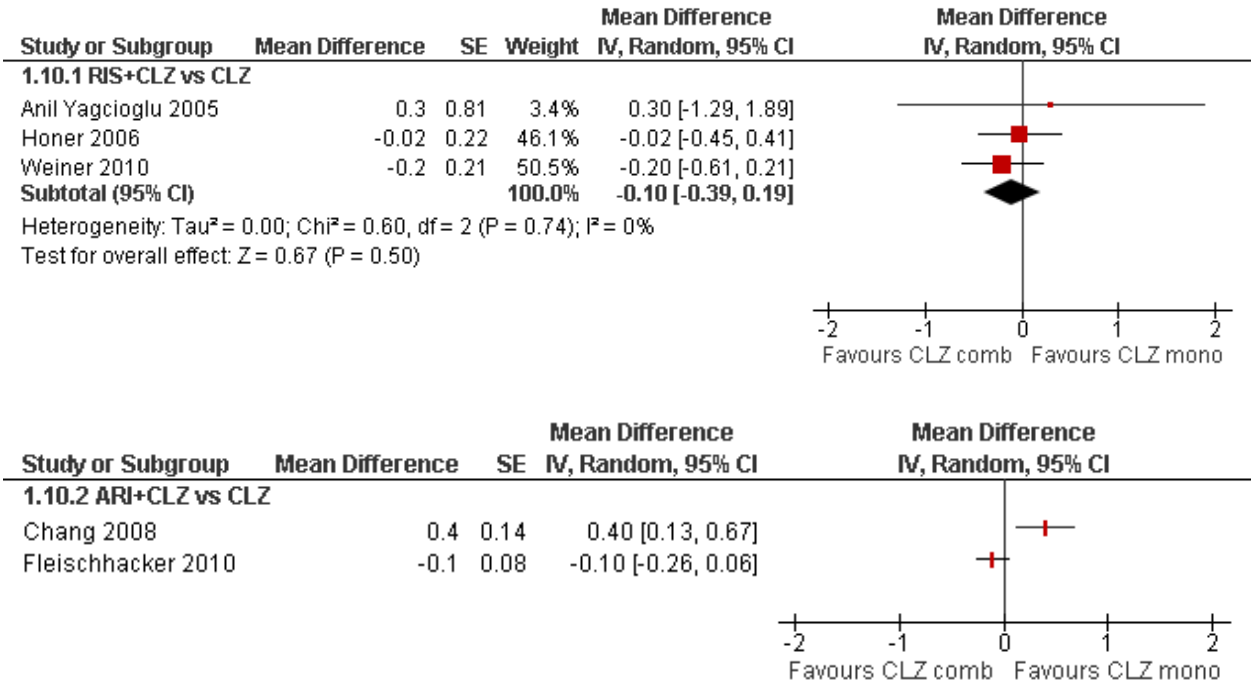


Figure A1.10: Forest plot for CLZ comb versus CLZ mono: CGI-S (WMD of changes from baseline (95% CI)) — subgroup by drug *




* (ARI+CLZ versus CLZ) was not pooled due to high heterogeneity

Figure A1.11: Forest plot for CLZ comb versus CLZ mono: GAF (WMD of changes from baseline (95% CI)) — reference case

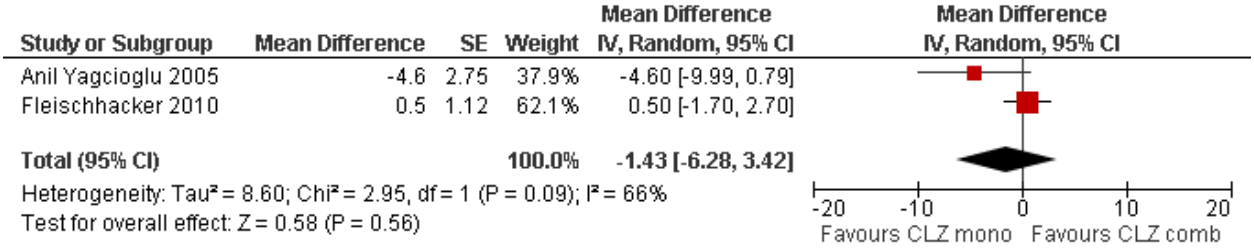


Figure A1.12: Forest plot for CLZ comb versus CLZ mono: GAF (WMD of changes from baseline (95% CI)) — subgroup by drug

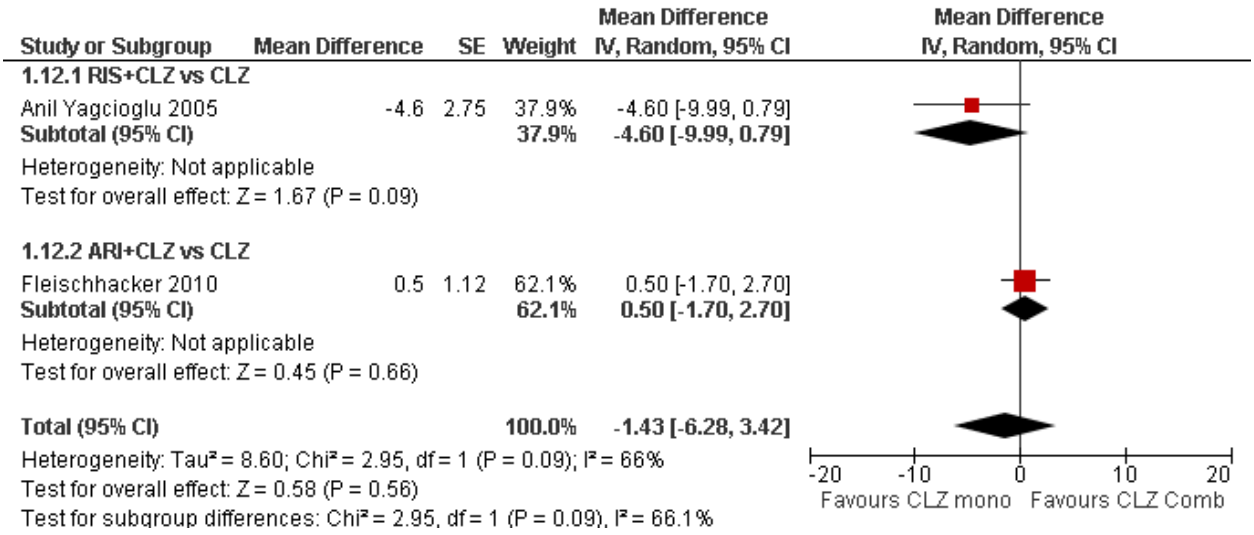



Figure A1.13: Forest plot for CLZ comb versus CLZ mono: Response rate (RR (95% CI)) — reference case

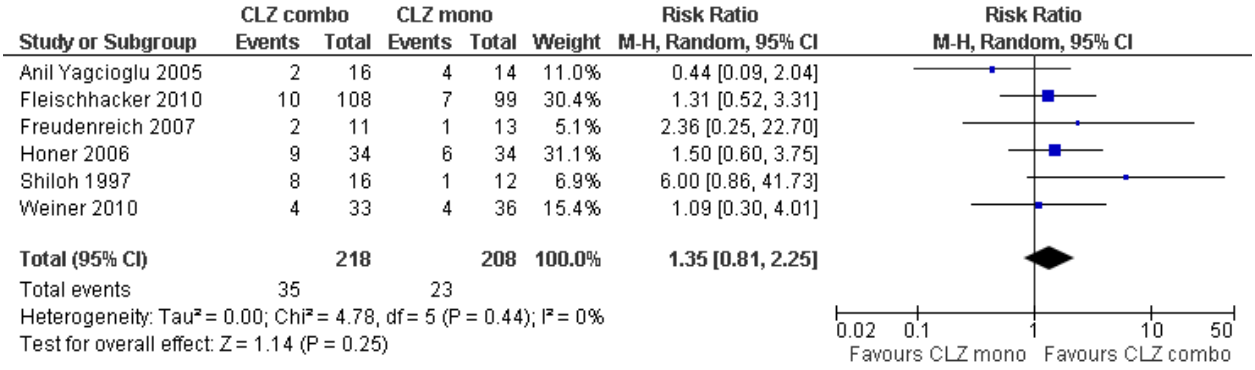


Figure A1.14: Forest plot for CLZ comb versus CLZ mono: Response rate (RR (95% CI)) — subgroup by drug

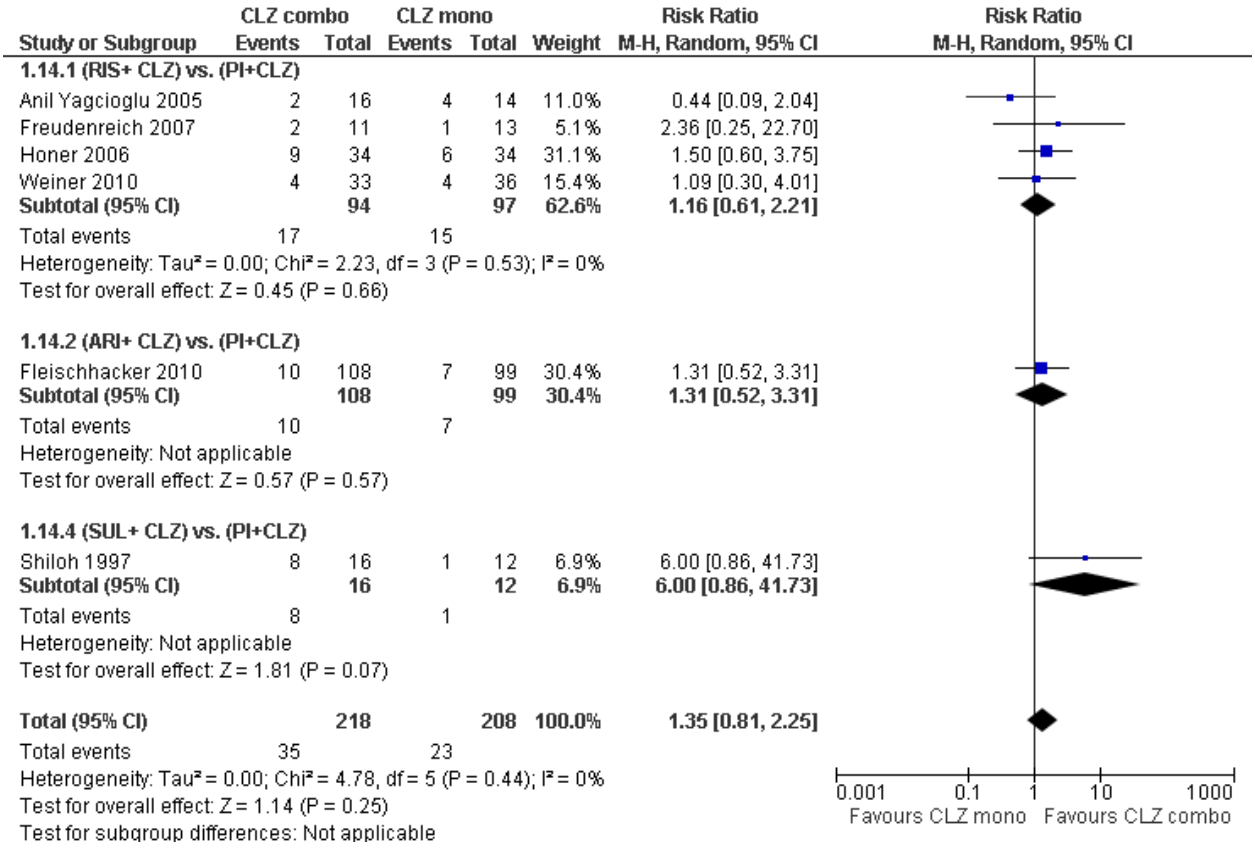



Figure A1.15: Forest plot for CLZ comb versus CLZ mono: Persistence with therapy (RR (95% CI)) — reference case

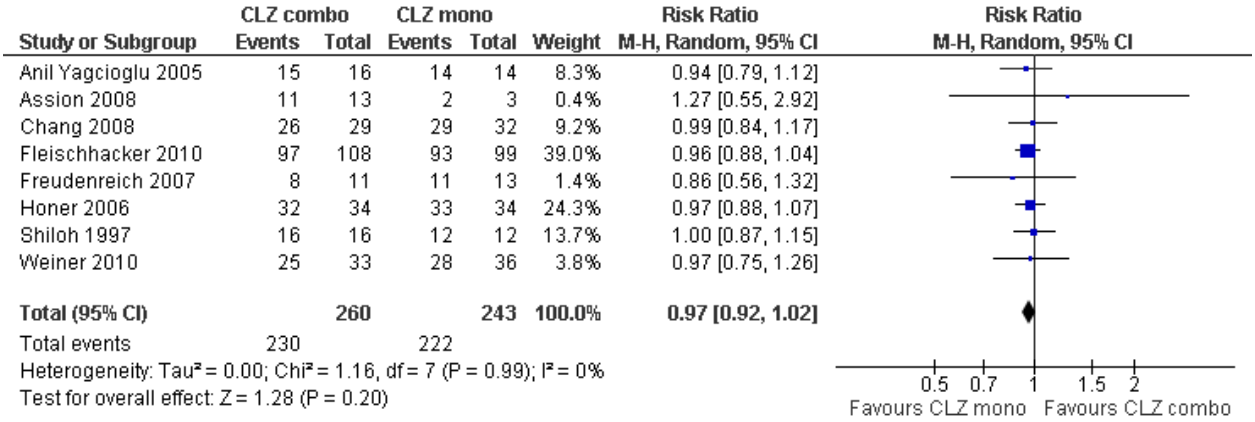


Figure A1.16: Forest plot for CLZ comb versus CLZ mono: Persistence with therapy (RR (95% CI)) — subgroup by drug

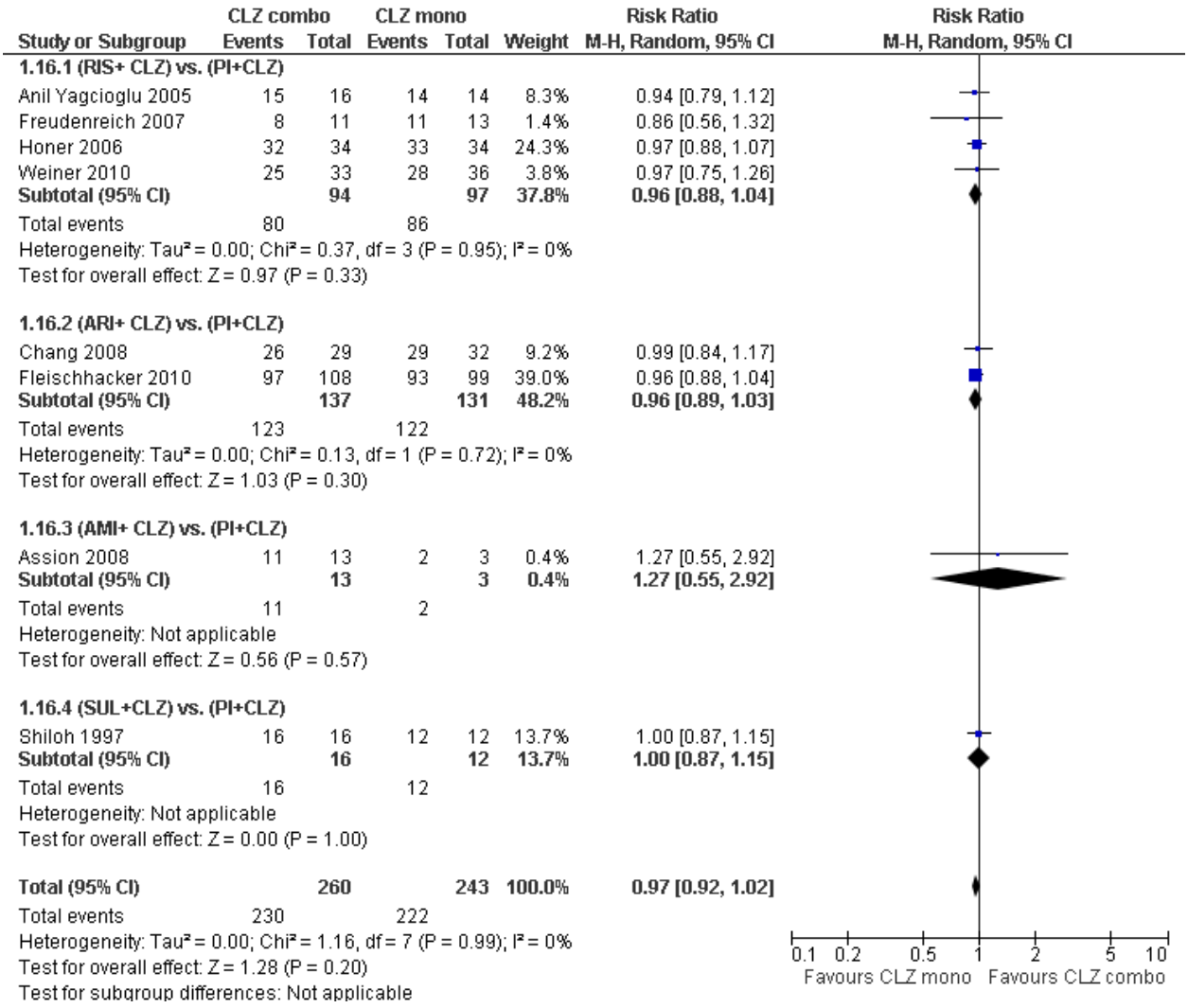



Figure A1.17: Forest plot for CLZ comb versus CLZ mono: Serious adverse events (RR (95% CI)) — reference case

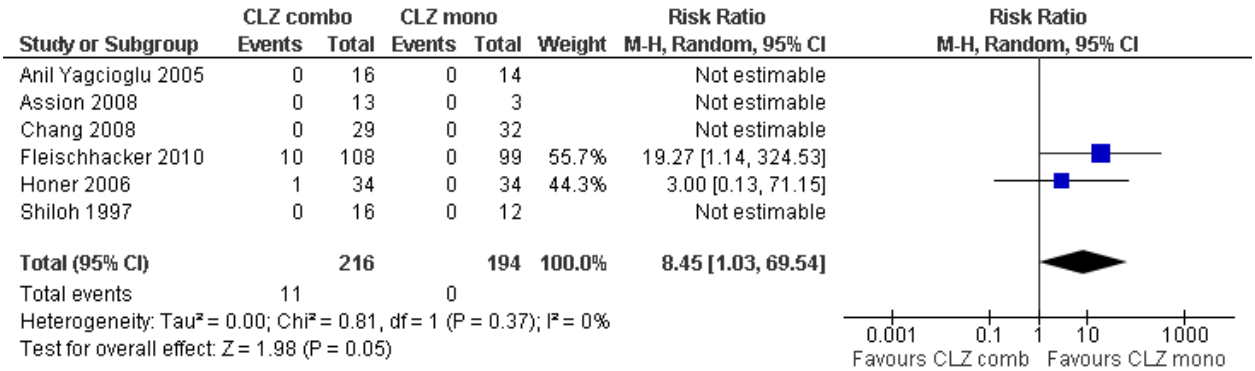


Figure A1.18: Forest plot for CLZ comb versus CLZ mono: Serious adverse events (RR (95% CI)) — subgroup by drug

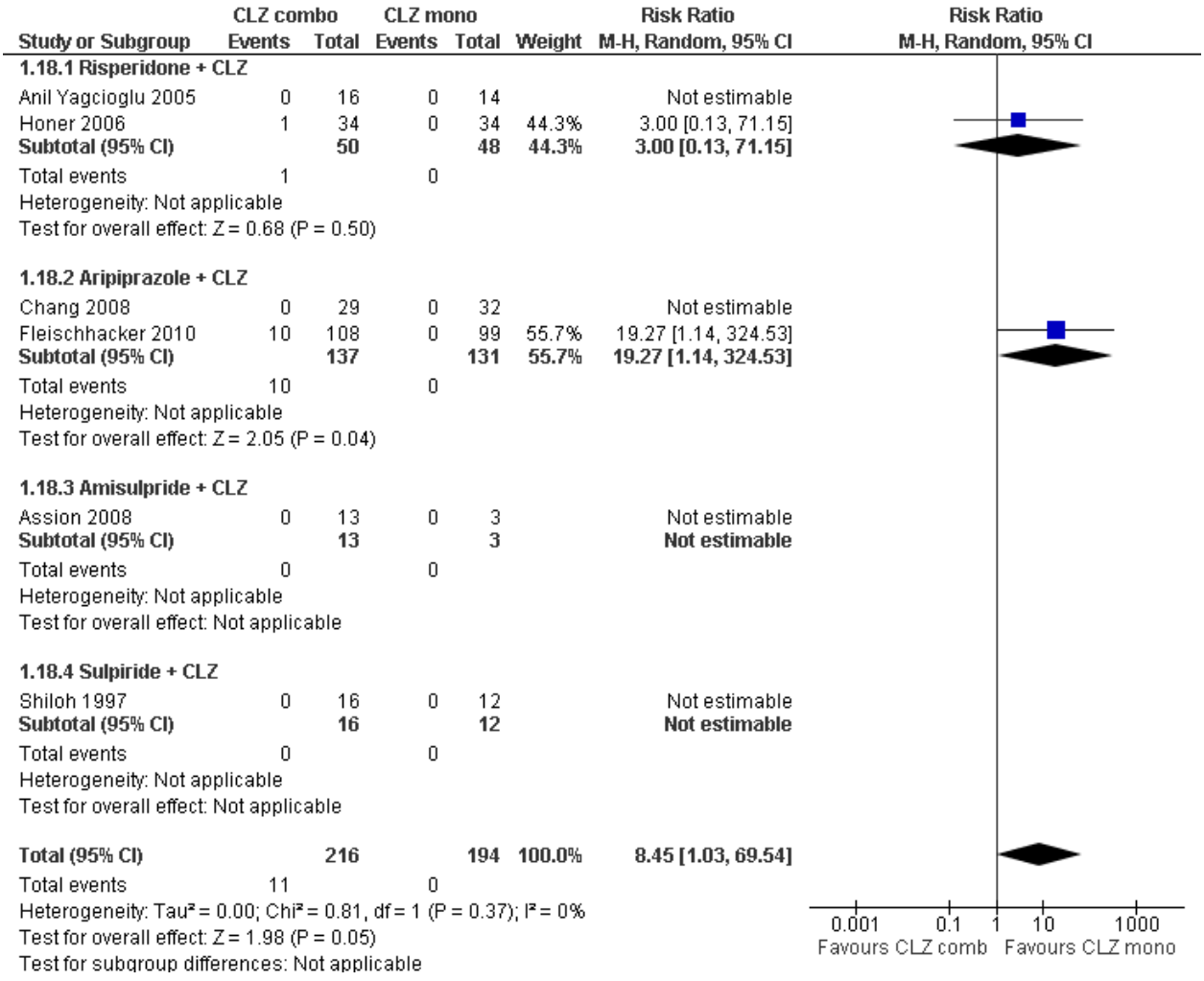



Figure A1.19: Forest plot for CLZ comb versus CLZ mono: Withdrawals due to AEs (RR (95% CI)) — reference case

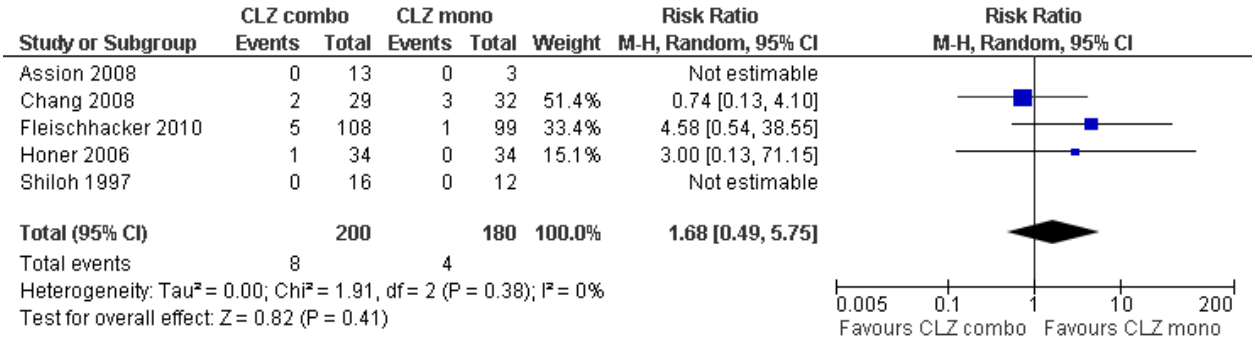


Figure A1.20: Forest plot for CLZ comb versus CLZ mono: Withdrawals due to AEs (RR (95% CI)) — subgroup by drug

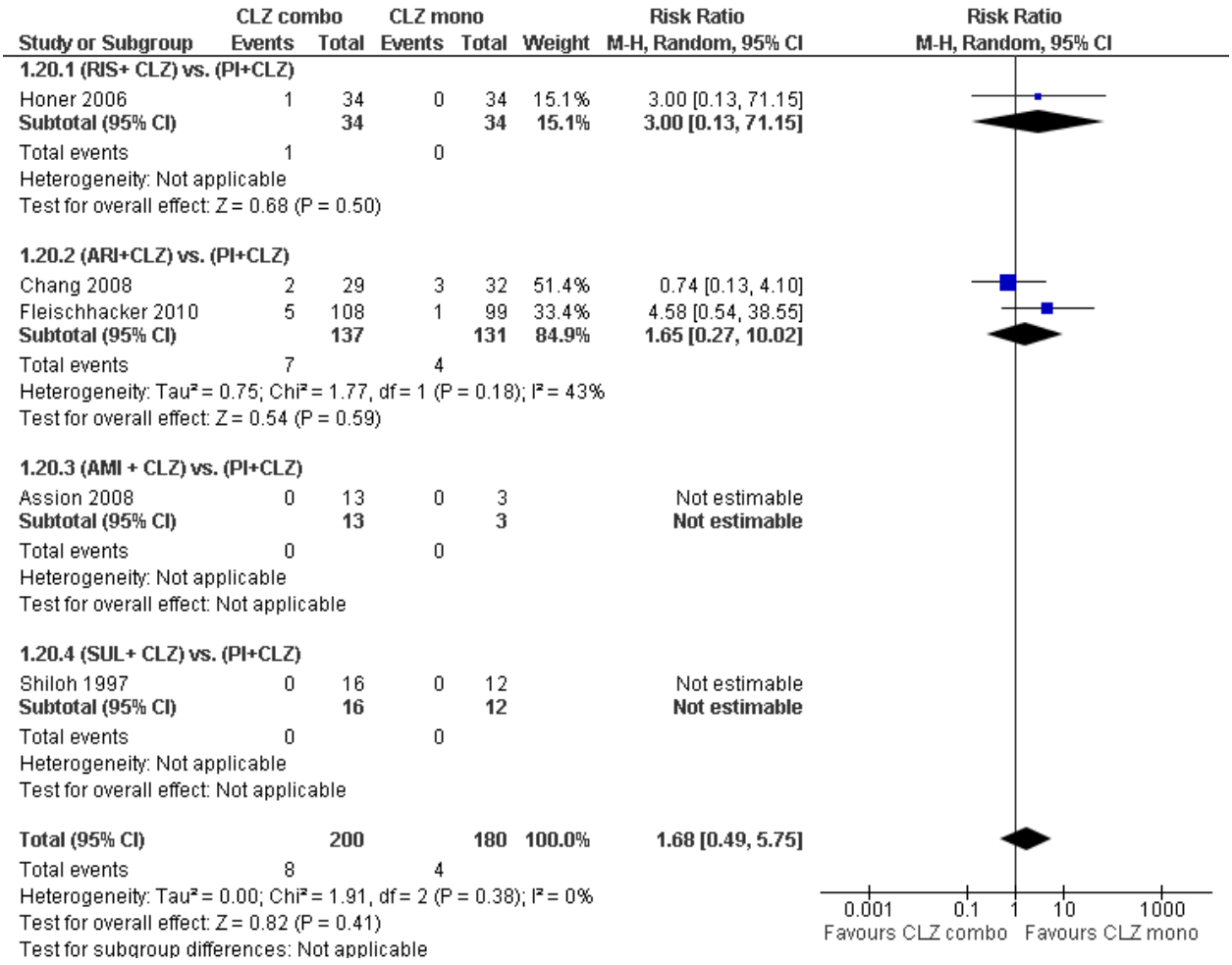



Figure A1.21: Forest plot for CLZ comb versus CLZ mono: All cause withdrawals (RR (95% CI)) — reference case

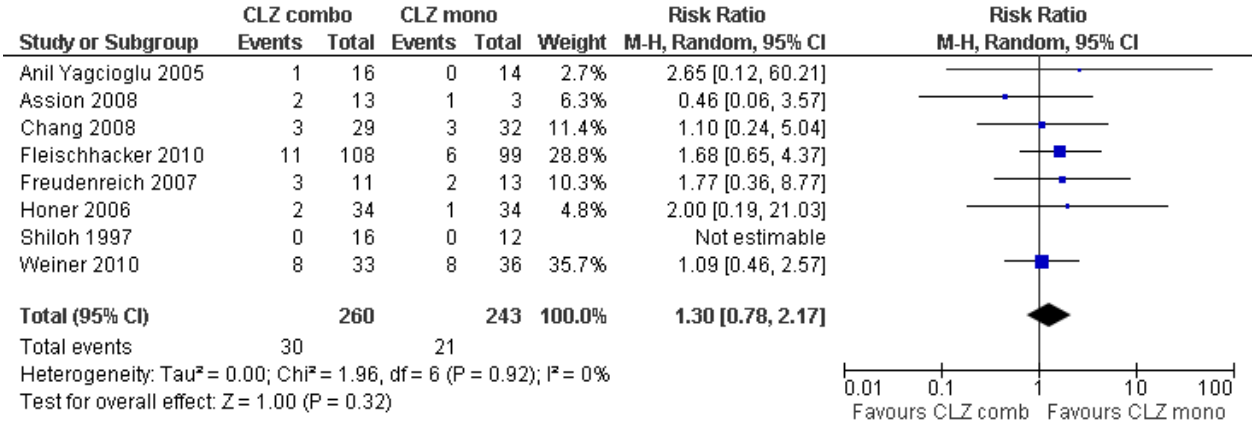


Figure A1.22: Forest plot for CLZ comb versus CLZ mono: All cause withdrawals (RR (95% CI)) — subgroup by drug

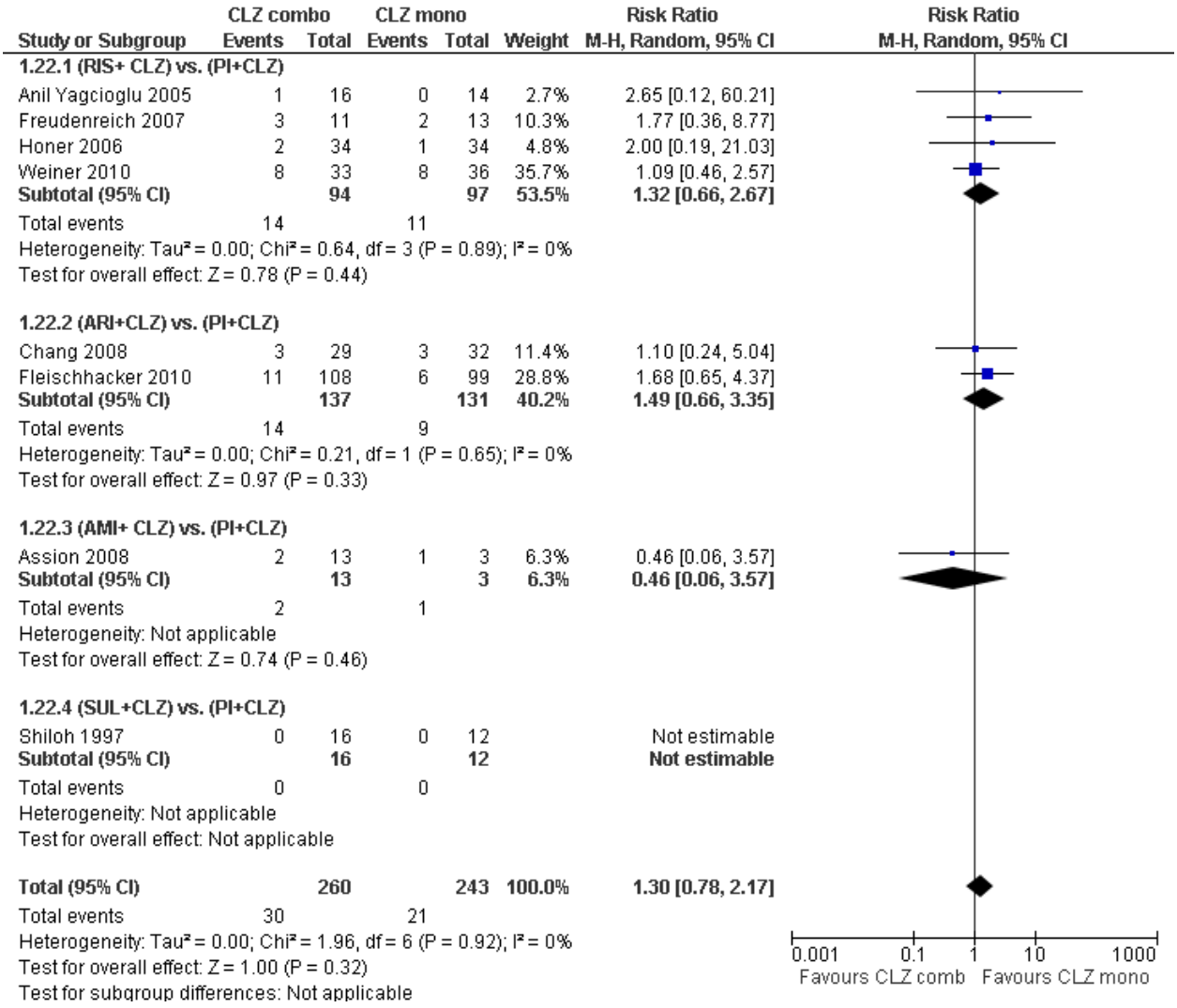



Figure A1.23: Forest plot for CLZ comb versus CLZ mono: Akathisia (RR (95% CI)) — reference case

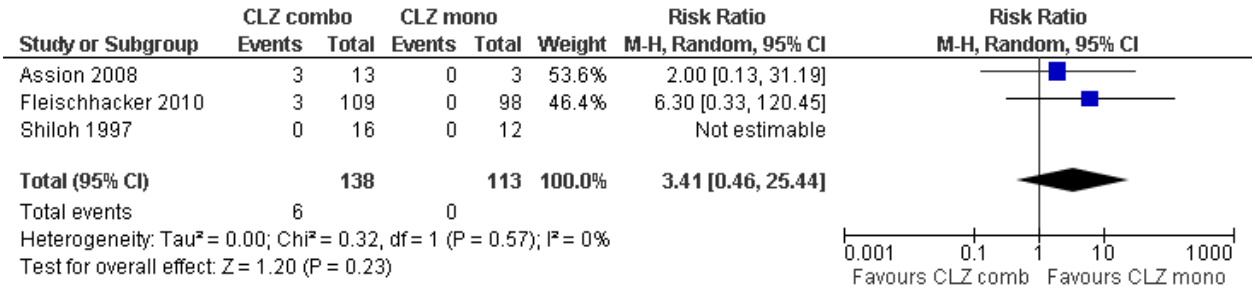


Figure A1.24: Forest plot for CLZ comb versus CLZ mono: Akathisia (RR (95% CI)) — subgroup by drug

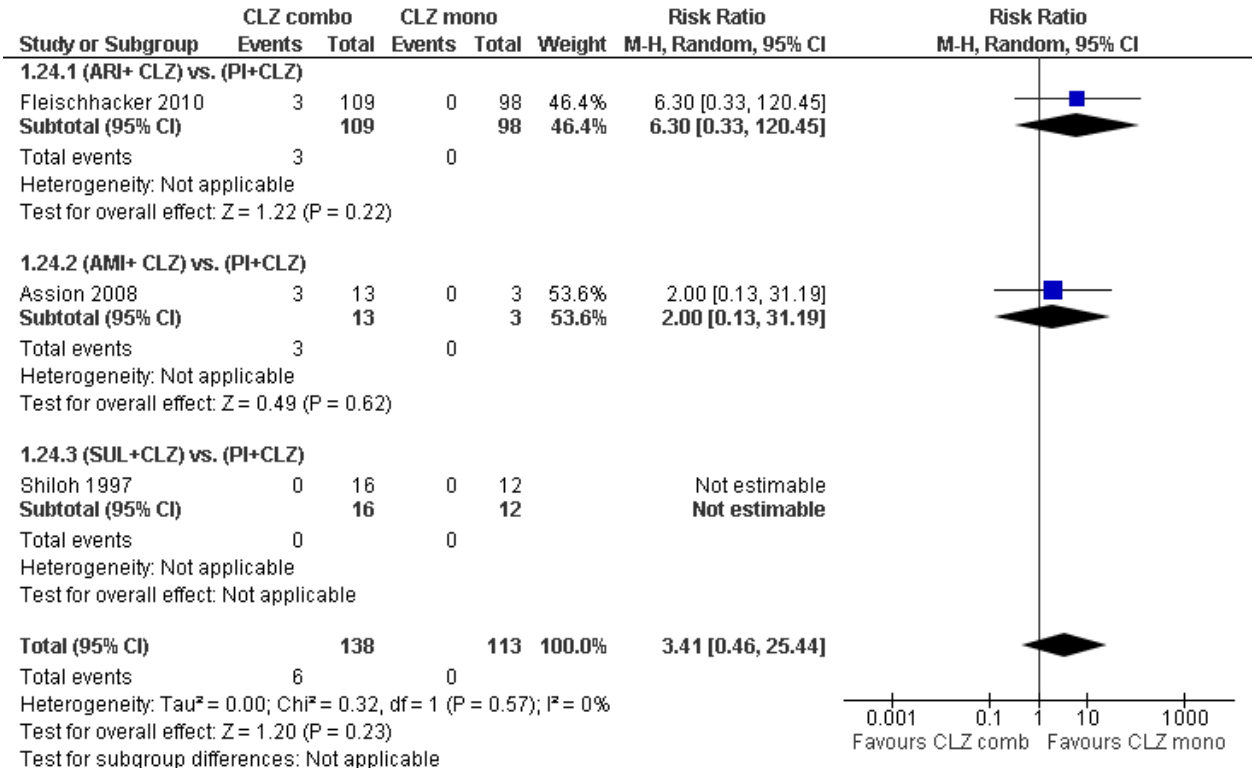



Figure A1.25: Forest plot for CLZ comb versus CLZ mono: Extrapyramidal effects/disorder (no. of pts) (RR (95% CI)) — reference case

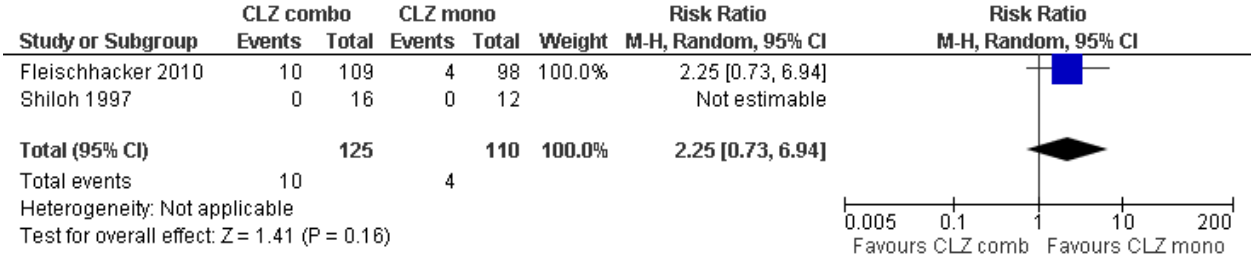
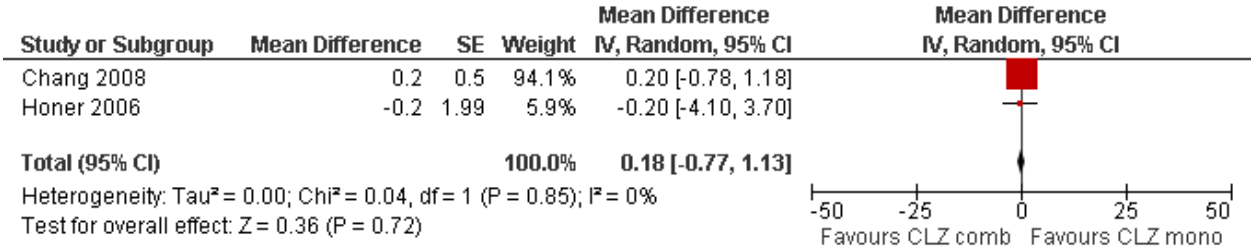



Figure A1.26: Forest plot for CLZ comb versus CLZ mono: EPS (ESRS, DIEPSS) (WMD of changes from baseline (95% CI))




*Results not pooled due to high heterogeneity.

Figure A1.27: Forest plot for CLZ comb versus CLZ mono: Parkinsonism (RR (95% CI)) — reference case

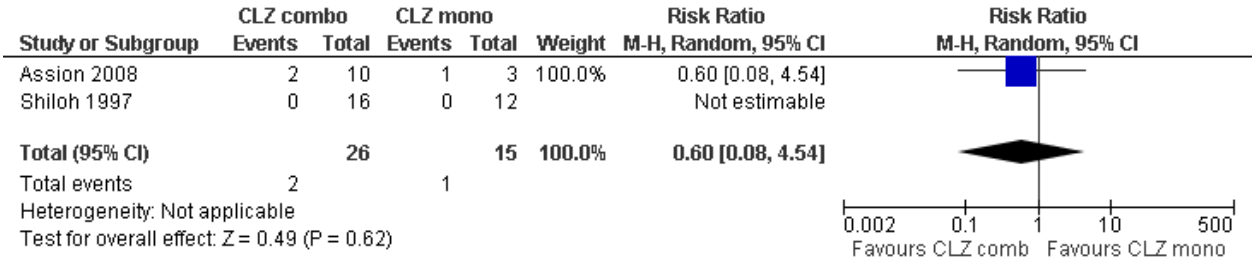



Figure A1.28: Forest plot for CLZ comb versus CLZ mono: AIMS (WMD of changes from baseline (95% CI)) — reference case

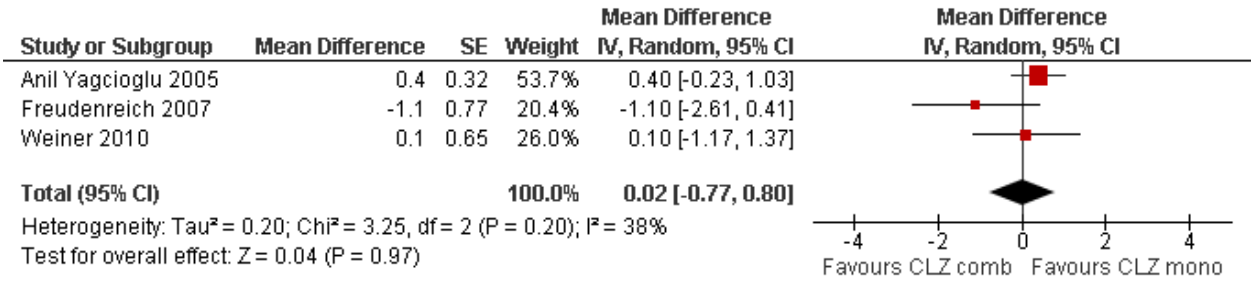



Figure A1.29: Forest plot for CLZ comb versus CLZ mono: BA(R)S (WMD of changes from baseline (95% CI)) — reference case

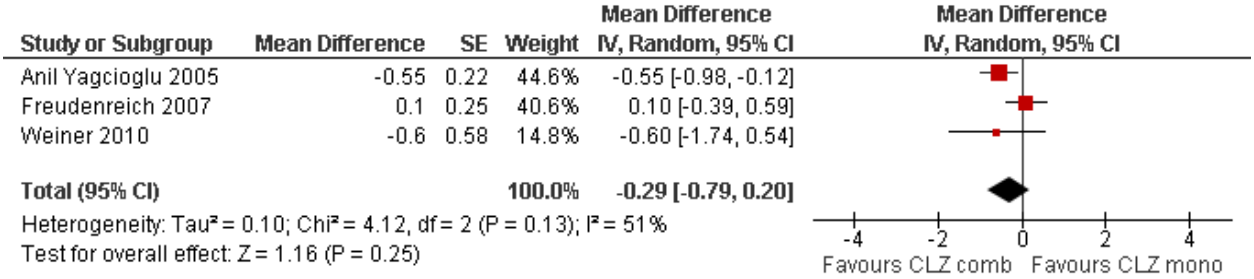



Figure A1.30: Forest plot for CLZ comb versus CLZ mono: SA(R)S (WMD of changes from baseline (95% CI)) — reference case

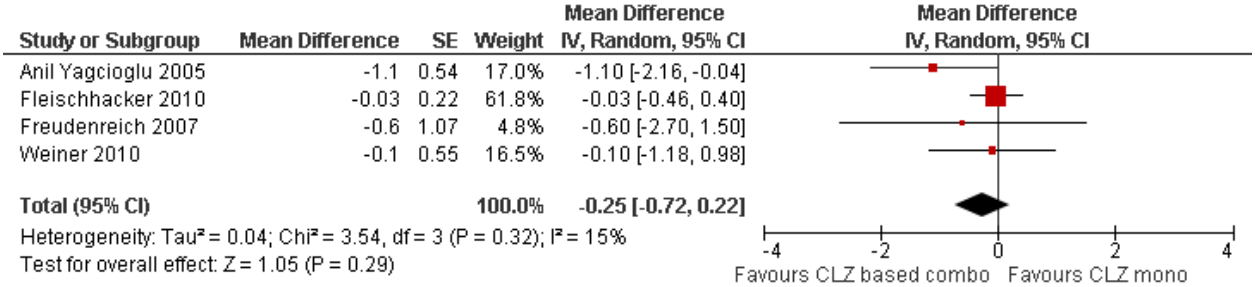


Figure A1.31: Forest plot for CLZ comb versus CLZ mono: SA(R)S (WMD of changes from baseline (95% CI)) — subgroup by drug

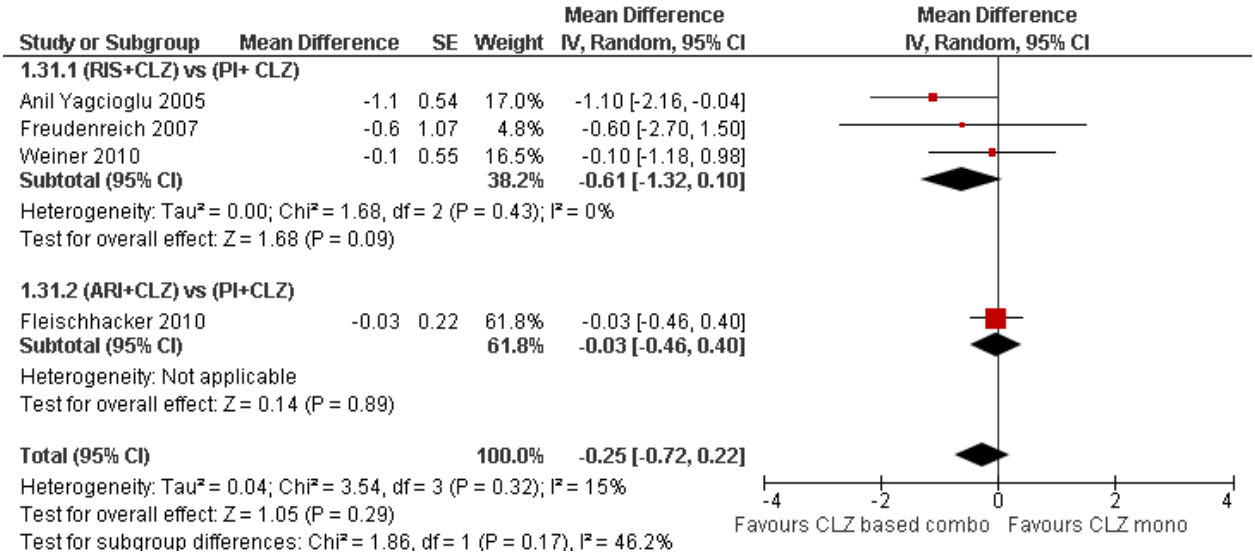
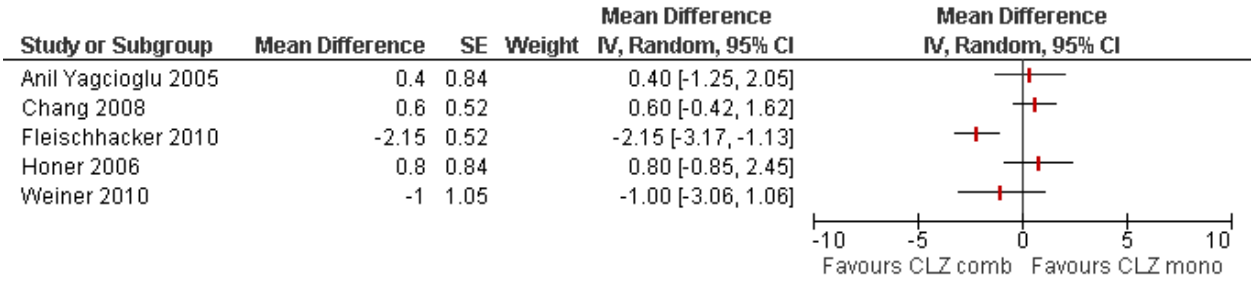
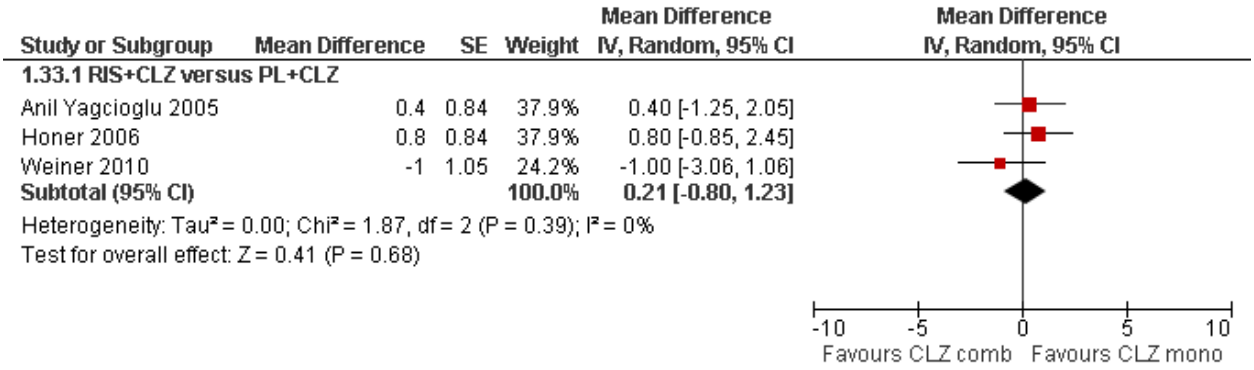


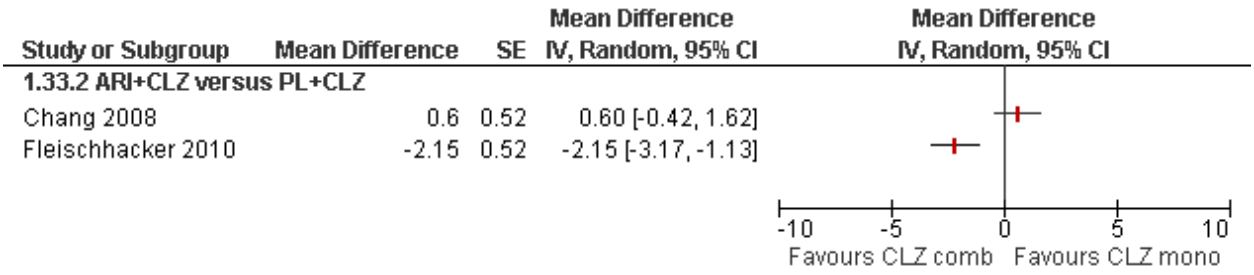

Figure A1.32: Forest plot for CLZ comb versus CLZ mono: Body weight (kg) (WMD of changes from baseline (95% CI)) — reference case




Results not pooled due to high heterogeneity.

Figure A1.33: Forest plot for CLZ comb versus CLZ mono: Body weight (kg) (WMD of changes from baseline (95% CI)) — subgroup by drug *






*(ARI+CLZ) versus (PL+CLZ) not pooled due to high heterogeneity

Figure A1.34: Forest plot for CLZ comb versus CLZ mono: Weight gain (no. of pts) (RR (95% CI)) — reference case

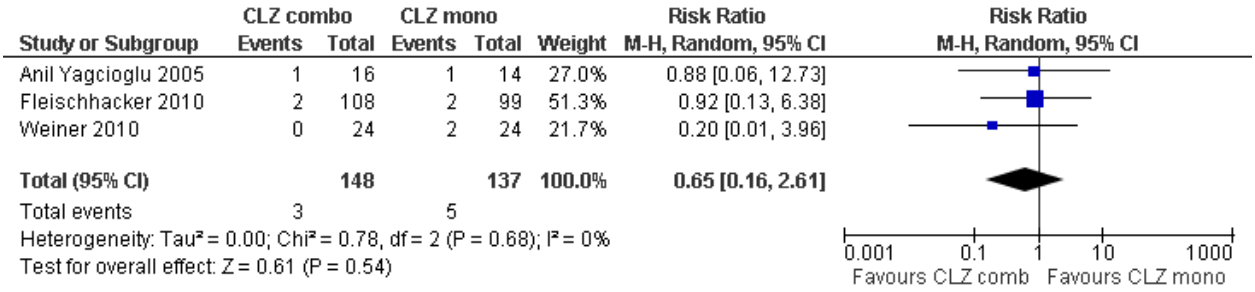



Figure A1.35: Forest plot for CLZ comb versus CLZ mono: Weight gain (no. of pts) (RR (95% CI)) — subgroup by drug

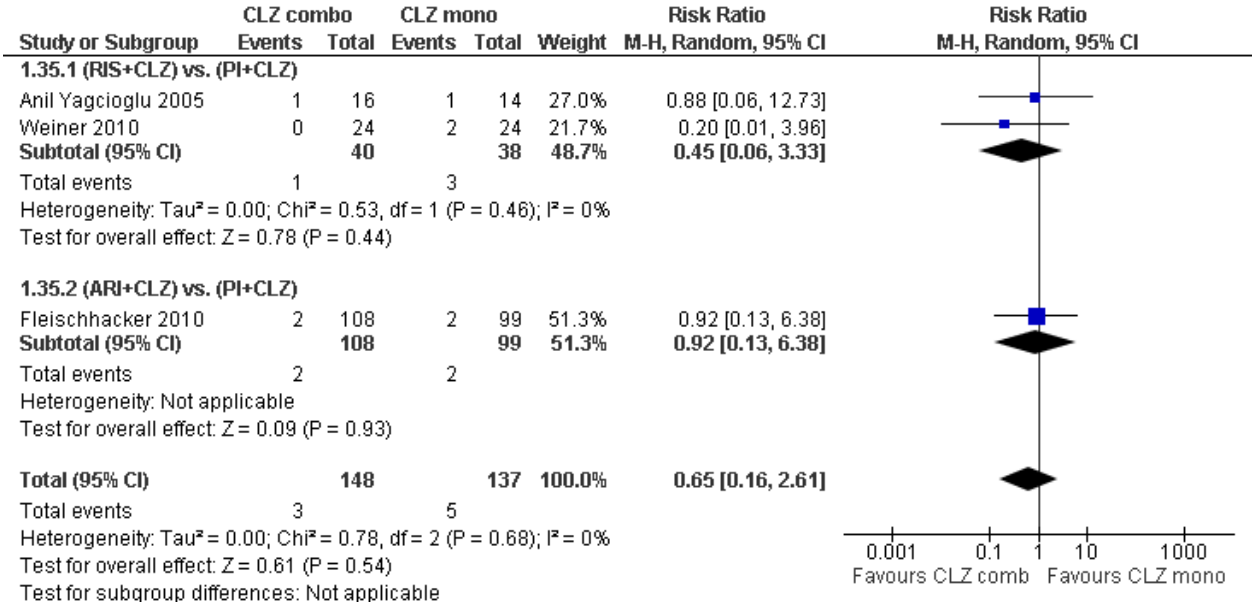


Figure A1.36: Forest plot for CLZ comb versus CLZ mono: Total cholesterol (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

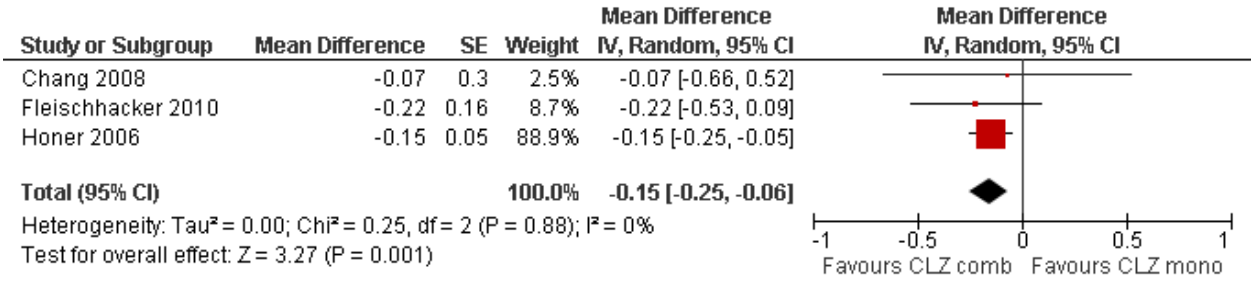



Figure A1.37: Forest plot for CLZ comb versus CLZ mono: HDL (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

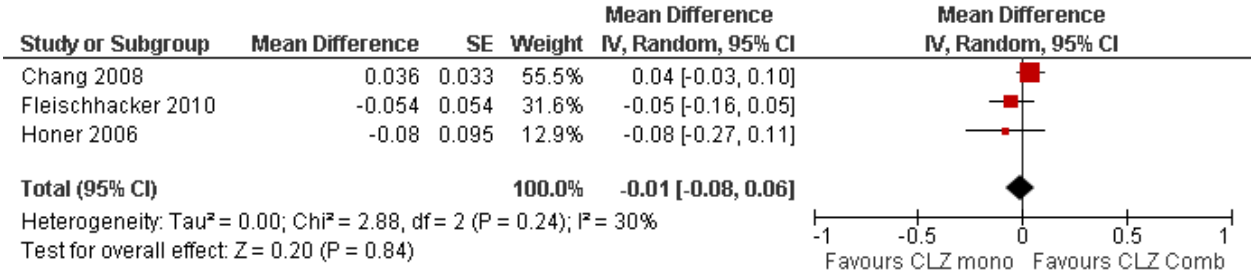



Figure A1.38: Forest plot for CLZ comb versus CLZ mono: LDL (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

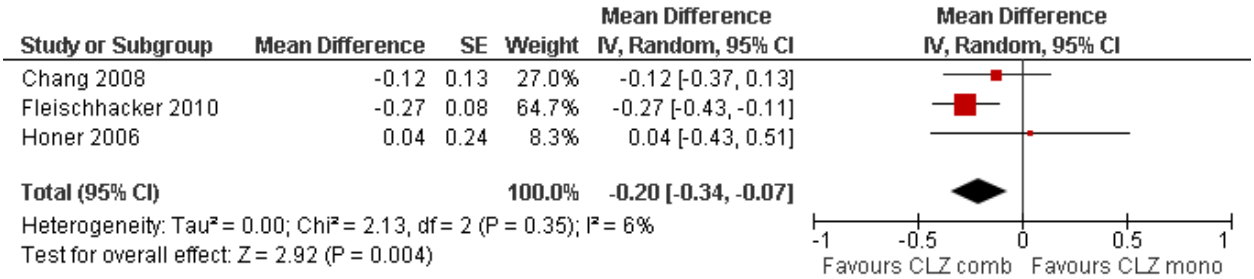



Figure A1.39: Forest plot for CLZ comb versus CLZ mono: Triglycerides (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

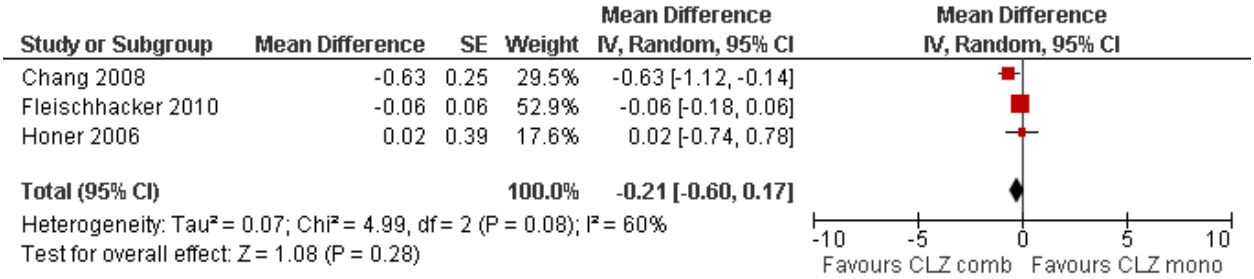


Figure A1.40: Forest plot for CLZ comb versus CLZ mono: FPG (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

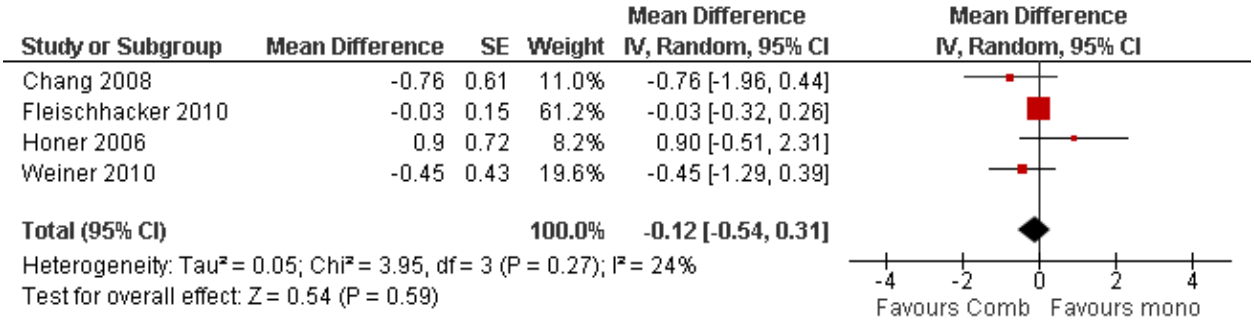
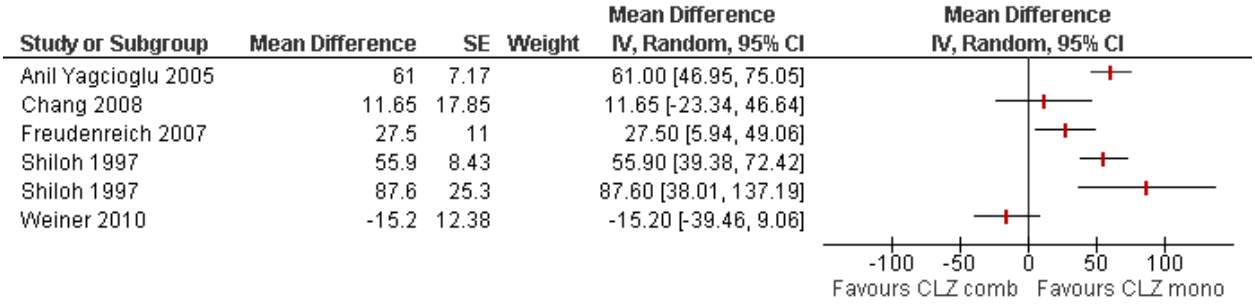



Figure A1.41: Forest plot for CLZ comb versus CLZ mono: Prolactin (ng/mL) (WMD of changes from baseline (95% CI)) — reference case




*Results not pooled due to high heterogeneity.

## 2. Forest Plot for Non-CLZ Combinations versus Non-CLZ Monotherapy (Figures A2.1 – A2.3)

Figure A2.1: Forest plot for non-CLZ comb versus non-CLZ mono: Persistence with therapy (RR (95% CI)) — subgroup by drug

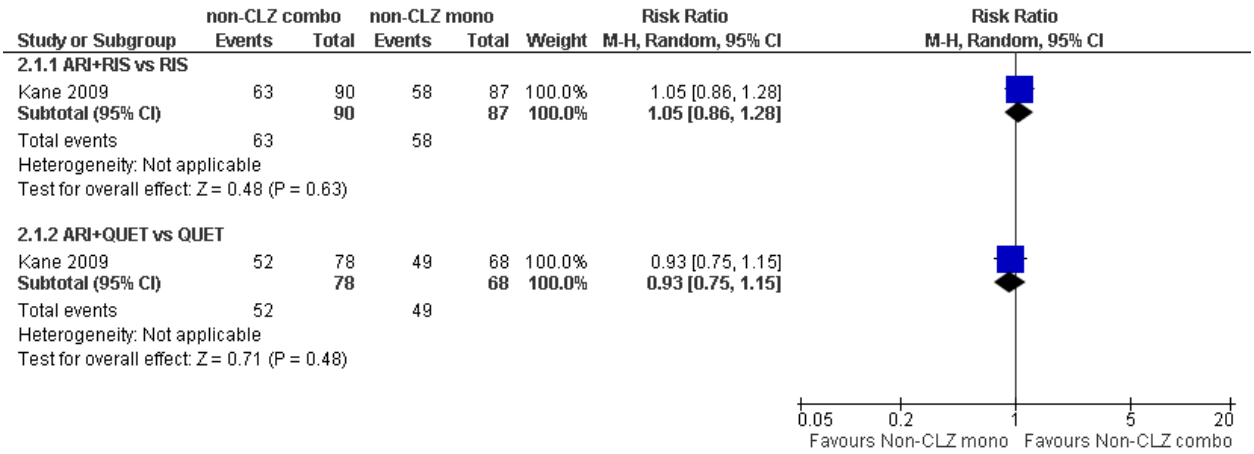


Figure A2.2: Forest plot for non-CLZ comb versus non-CLZ mono: All-cause withdrawals (RR (95% CI)) — subgroup by drug

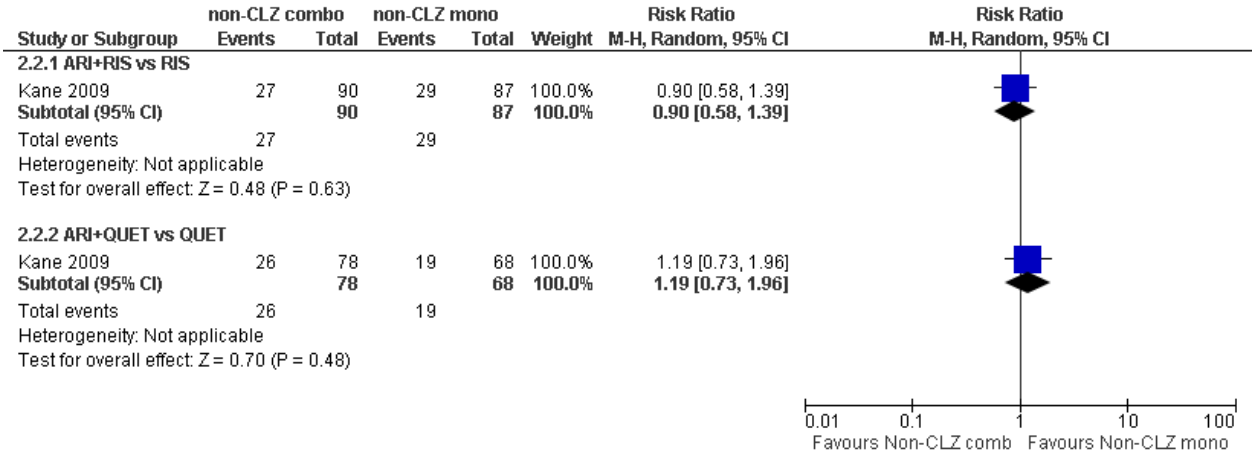
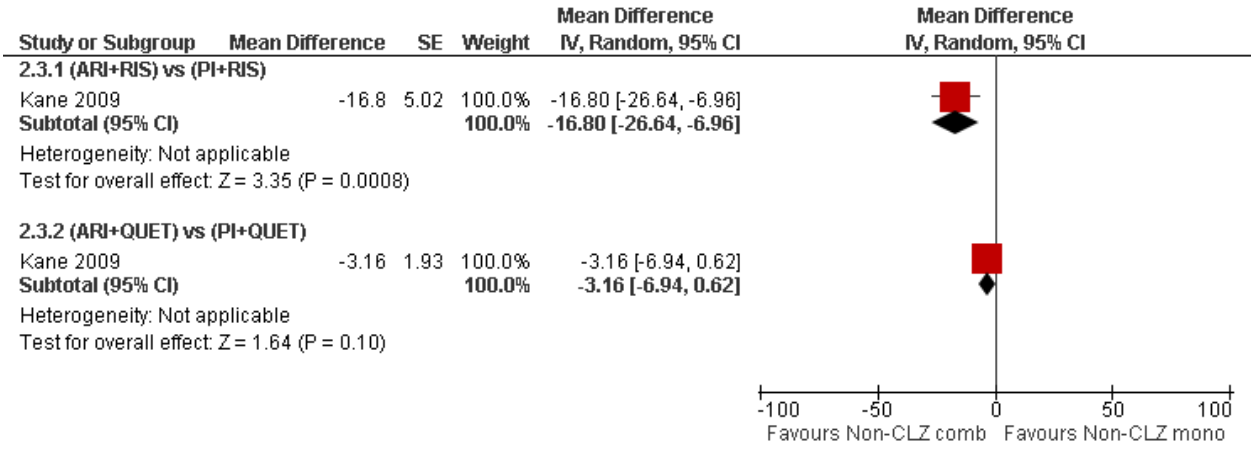



Figure A2.3: Forest plot for non-CLZ comb versus non-CLZ mono: Prolactin (ng/mL) (WMD of changes from baseline (95% CI)) – subgroup by drug



## 3. Forest Plot for High-Dose Non-CLZ AAP versus Standard-Dose CLZ Monotherapy (Figures A3.1 – A3.35)

Figure A3.1: Forest plot for high dose non-CLZ AAP versus std dose CLZ: PANSS-T (WMD of changes from baseline (95% CI)) — reference case

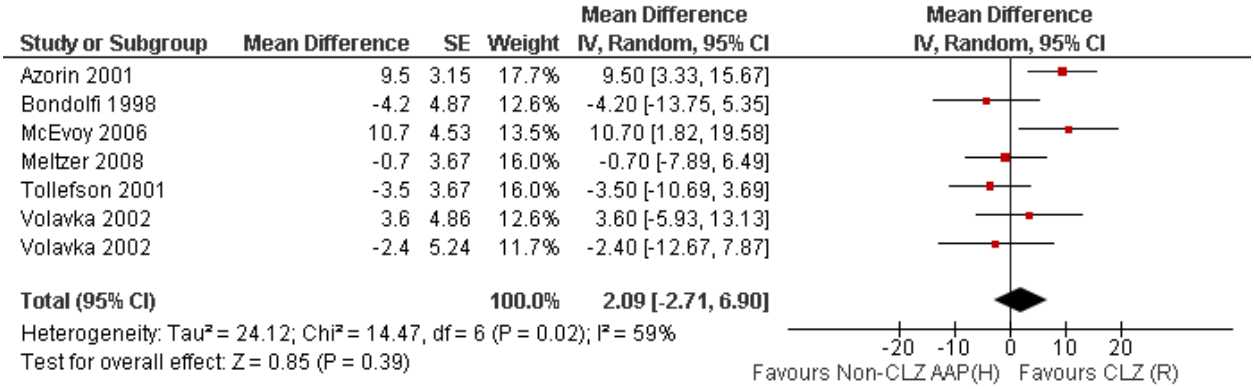



Figure A3.2: Forest plot for high dose non-CLZ AAP versus std dose CLZ: PANSS-T (WMD of changes from baseline (95% CI)) — Subgroup by drug

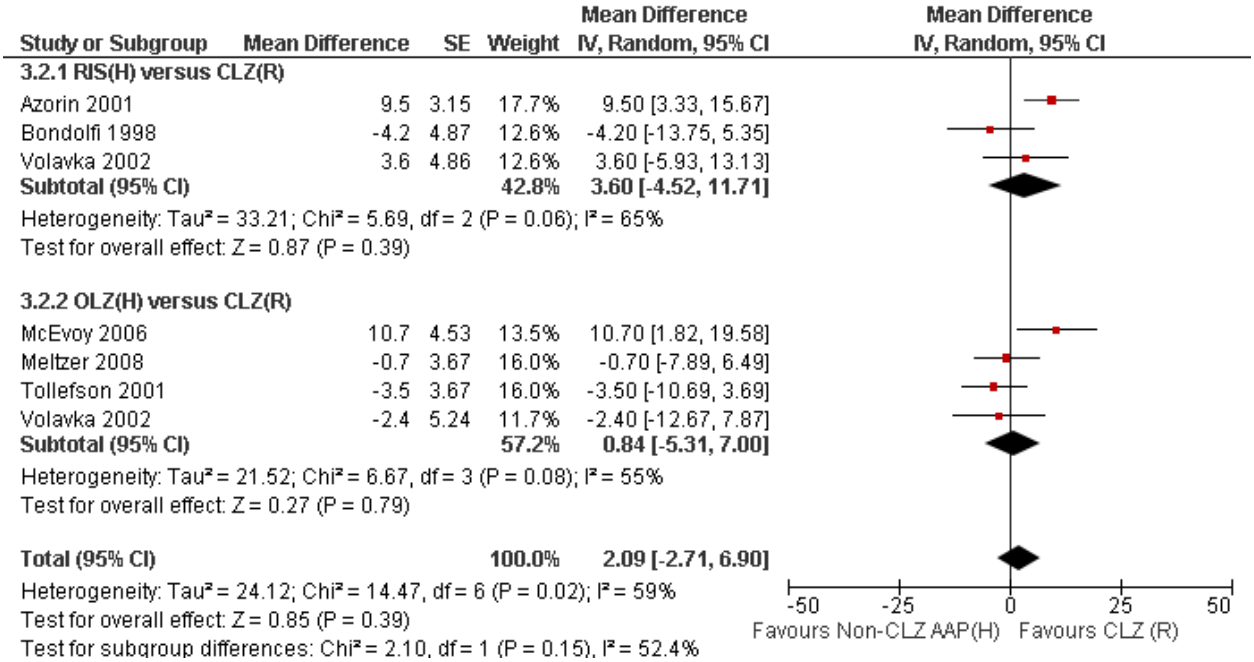


Figure A3.3: Forest plot for high dose non-CLZ AAP versus std dose CLZ: PANSS-P (WMD of changes from baseline (95% CI)) — reference case

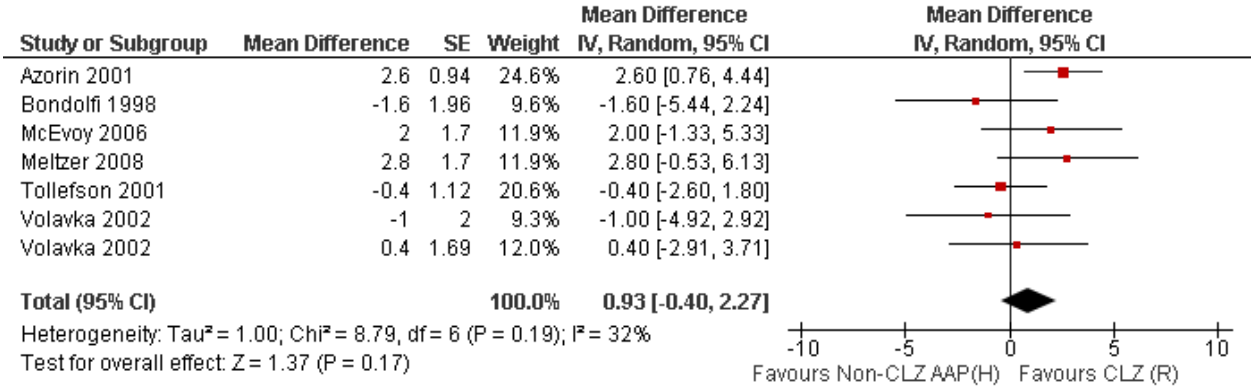



Figure A3.4: Forest plot for high dose non-CLZ AAP versus std dose CLZ: PANSS-P (WMD of changes from baseline (95% CI)) — subgroup by drug

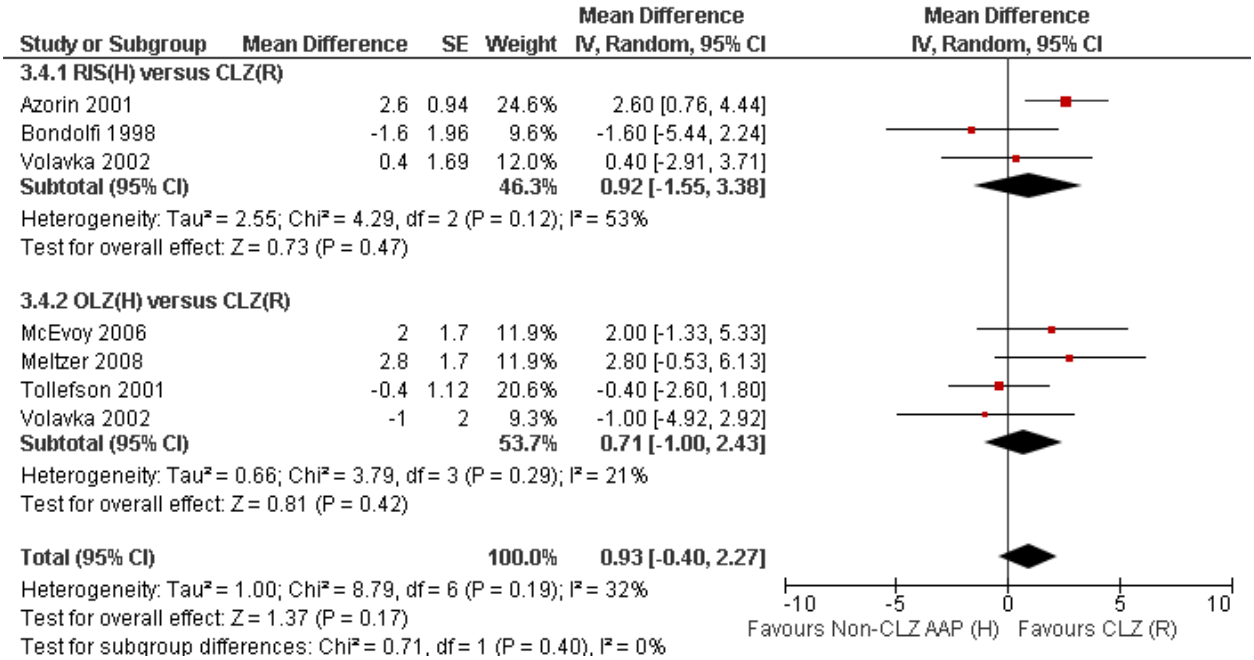


Figure A3.5: Forest plot for high dose non-CLZ AAP versus std dose CLZ: PANSS-N (WMD of changes from baseline (95% CI)) — reference case

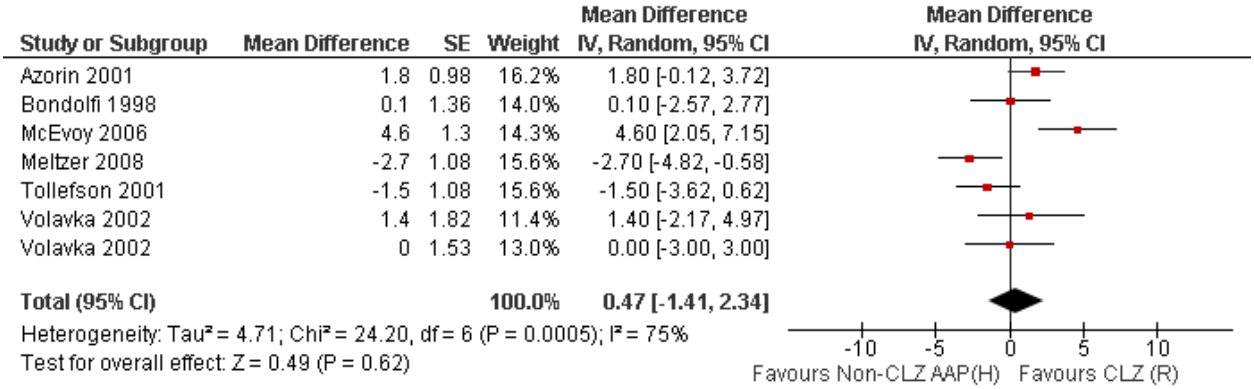
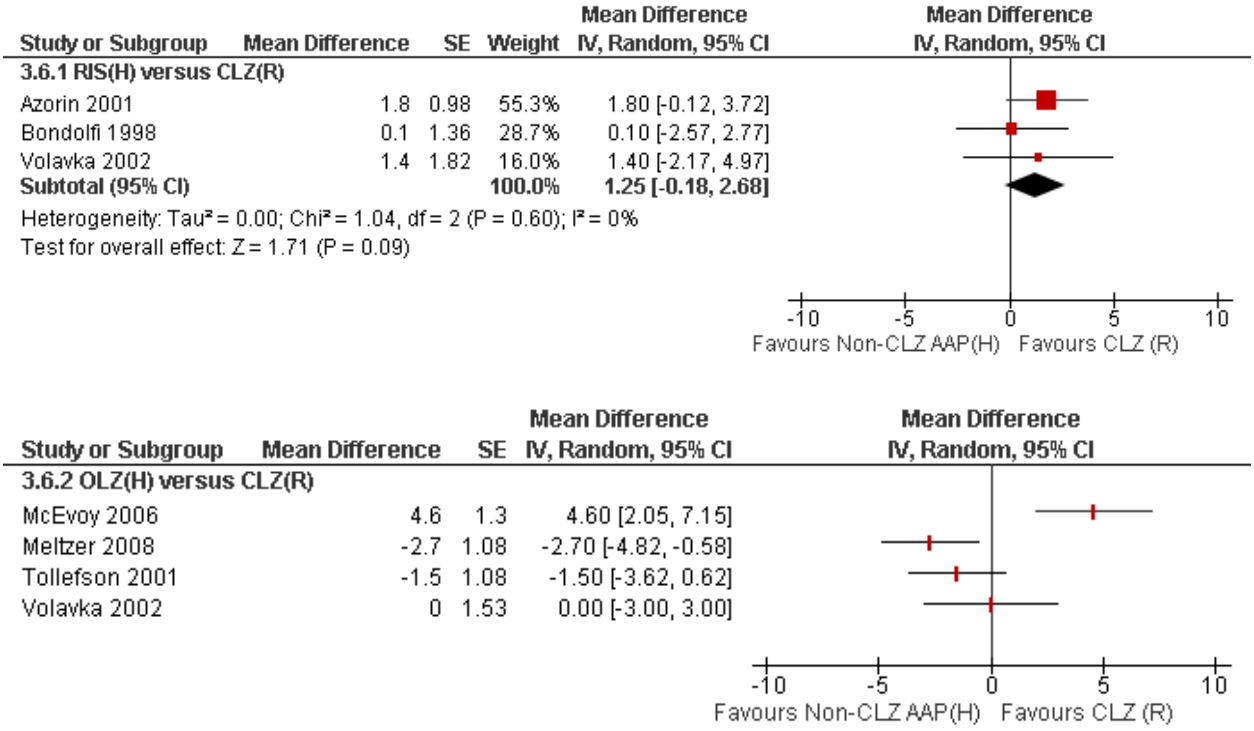
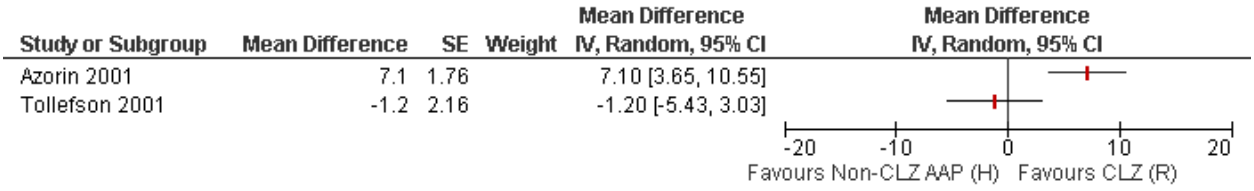



Figure A3.6: Forest plot for high dose non-CLZ AAP versus std dose CLZ: PANSS-N (WMD of changes from baseline (95% CI)) — subgroup by drug*



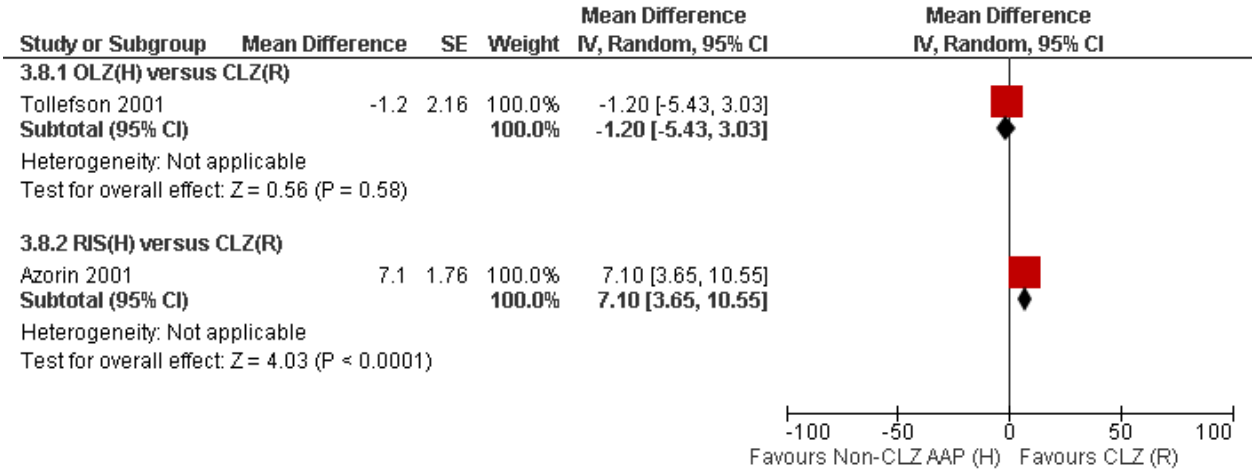

*(OLZ(H) versus CLZ(R) not pooled duo to high heterogeneity

Figure A3.7: Forest plot for high dose non-CLZ AAP versus std dose CLZ: BPRS (WMD of changes from baseline (95% CI)) — reference case




Results not pooled due to high heterogeneity.

Figure A3.8: Forest plot for high dose non-CLZ AAP versus std dose CLZ: BPRS (WMD of changes from baseline (95% CI)) — subgroup by drug




Results not pooled due to high heterogeneity.

Figure A3.9: Forest plot for high dose non-CLZ AAP versus std dose CLZ: CGI-I endpoint diff (WMD of changes from baseline (95% CI)) — adolescent study added

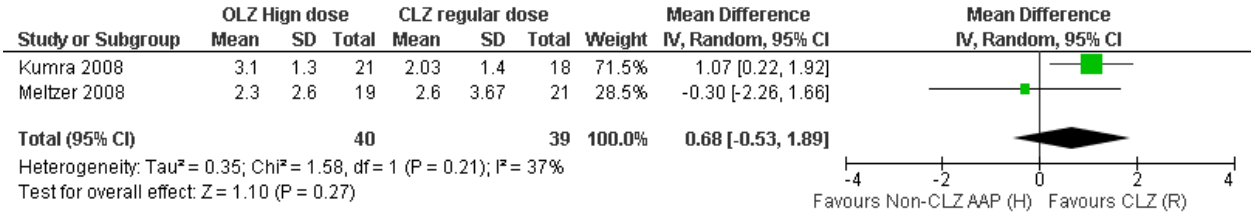


Figure A3.10: Forest plot for high dose non-CLZ AAP versus std dose CLZ: CGI-S (WMD of changes from baseline (95% CI)) — reference case

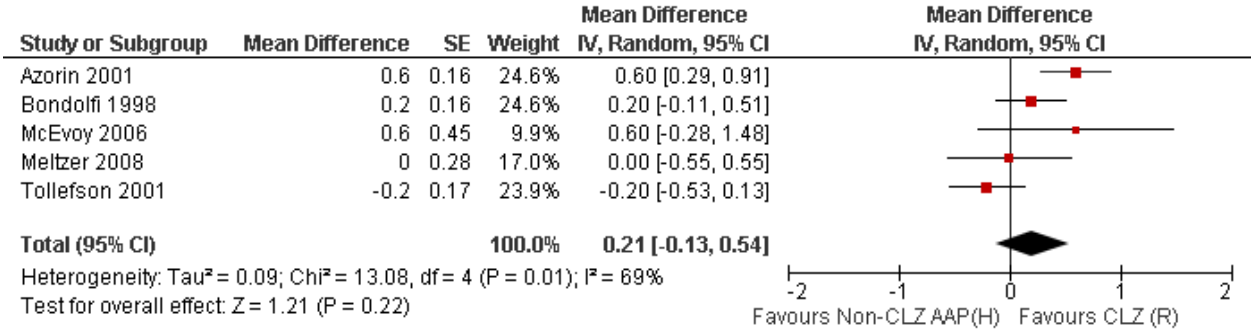



Figure A3.11: Forest plot for high dose non-CLZ AAP versus std dose CLZ: CGI-S (WMD of changes from baseline (95% CI)) — subgroup by drug

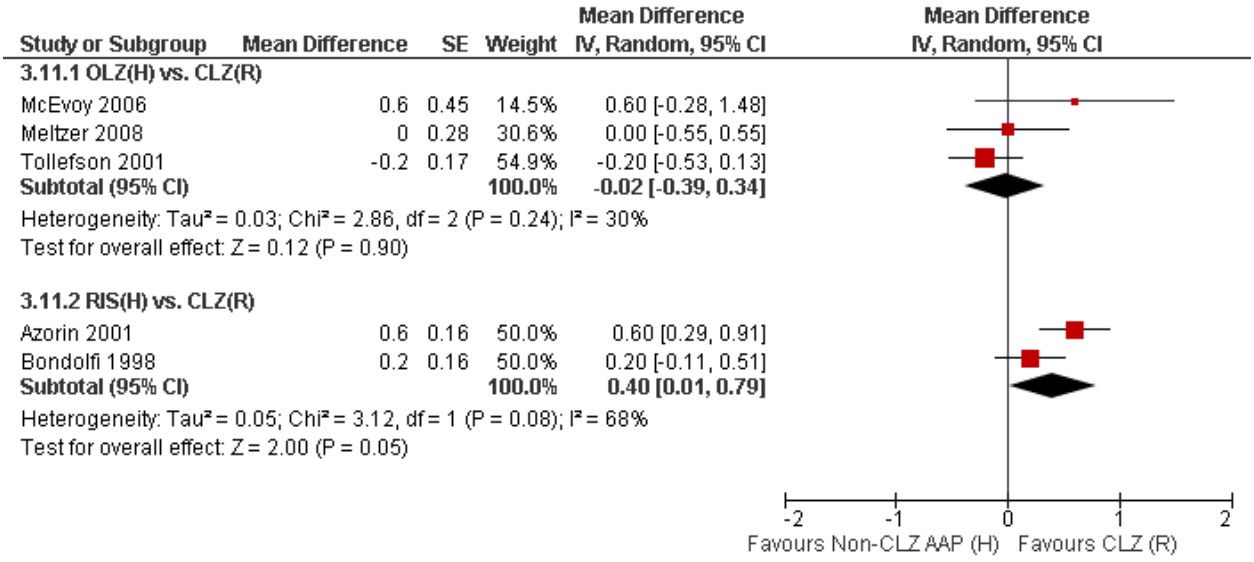



Figure A3.12: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Response rate (RR (95% CI)) — reference case

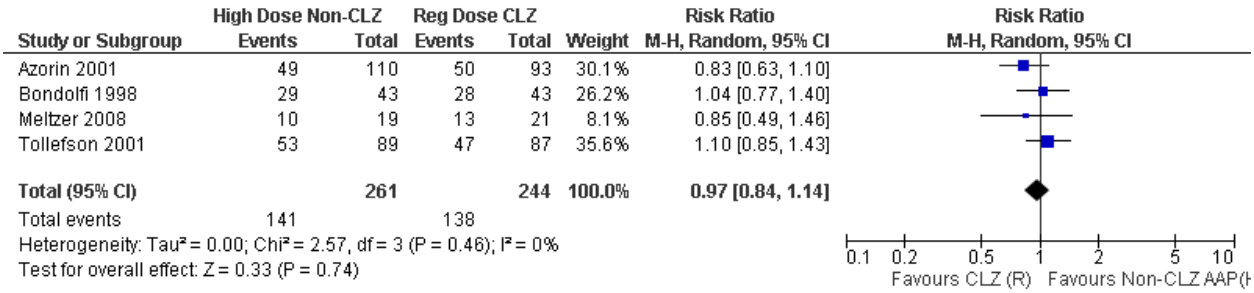


Figure A3.13: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Response rate (RR (95% CI)) — subgroup by drug

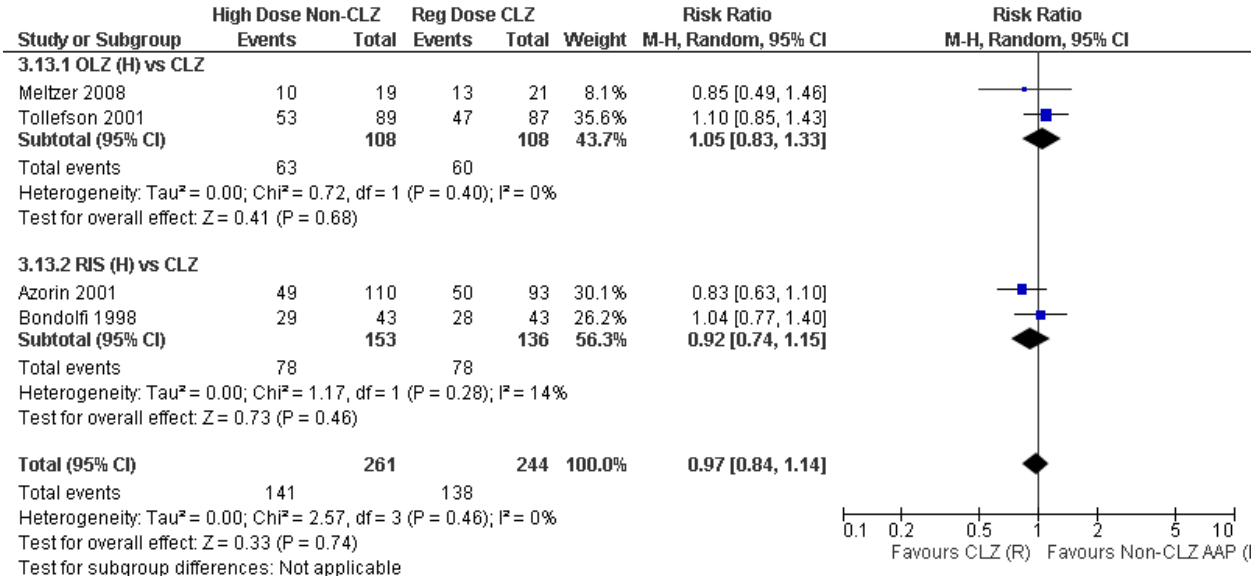



Figure A3.14: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Persistence with therapy (RR (95% CI)) — reference case

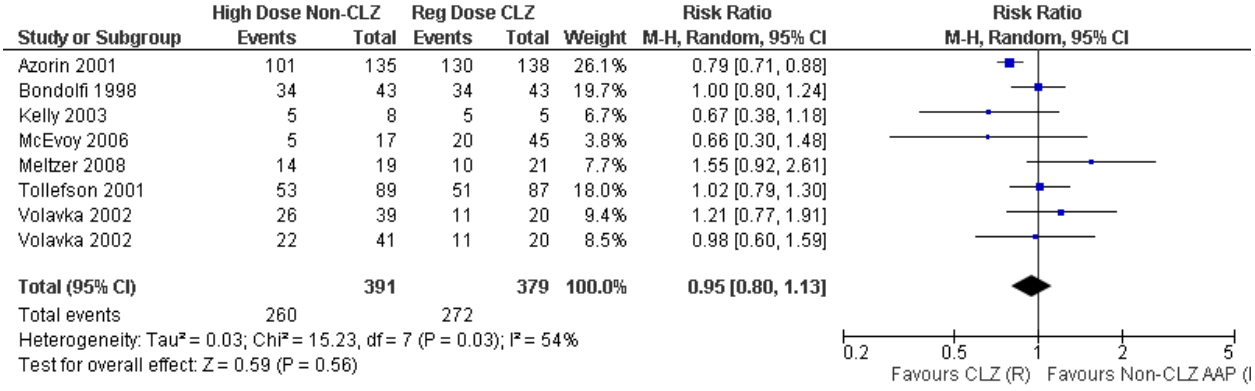


Figure A3.15: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Persistence with therapy (RR (95% CI)) — subgroup by drug

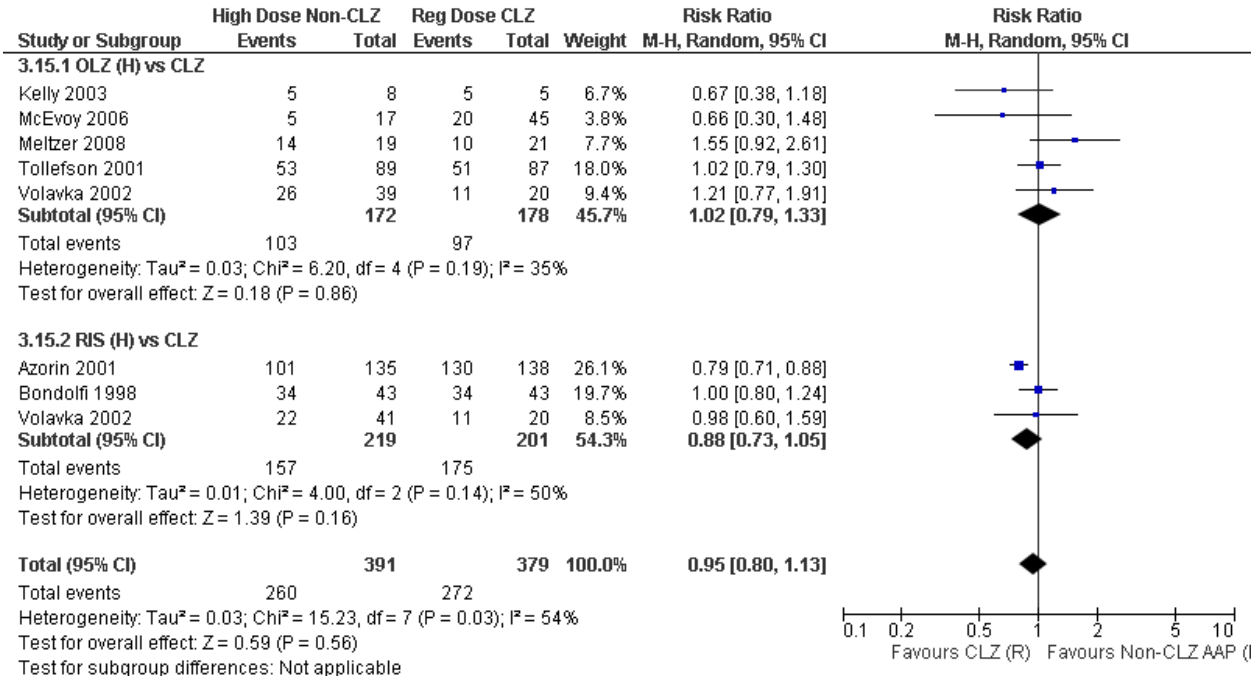



Figure A3.16: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Withdrawals due to AEs (RR (95% CI)) — reference case

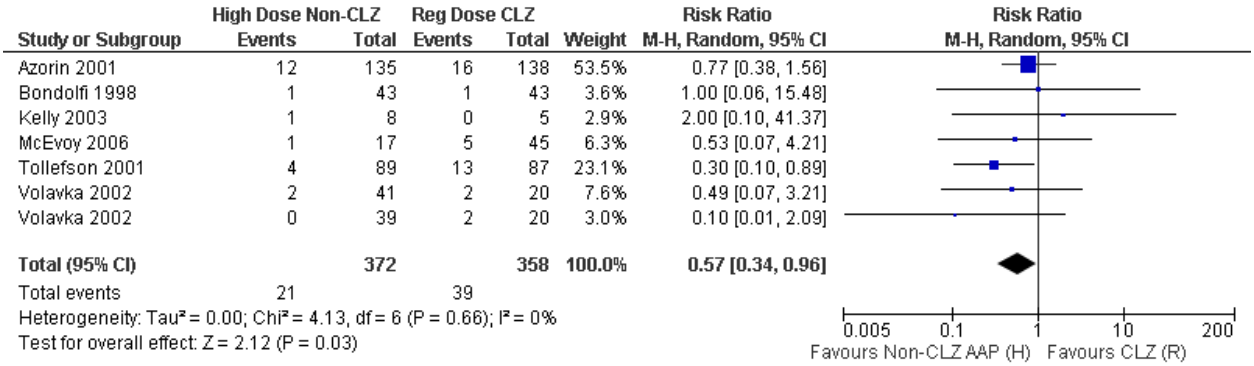


Figure A3.17: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Withdrawals due to AEs (RR (95% CI)) — subgroup by drug

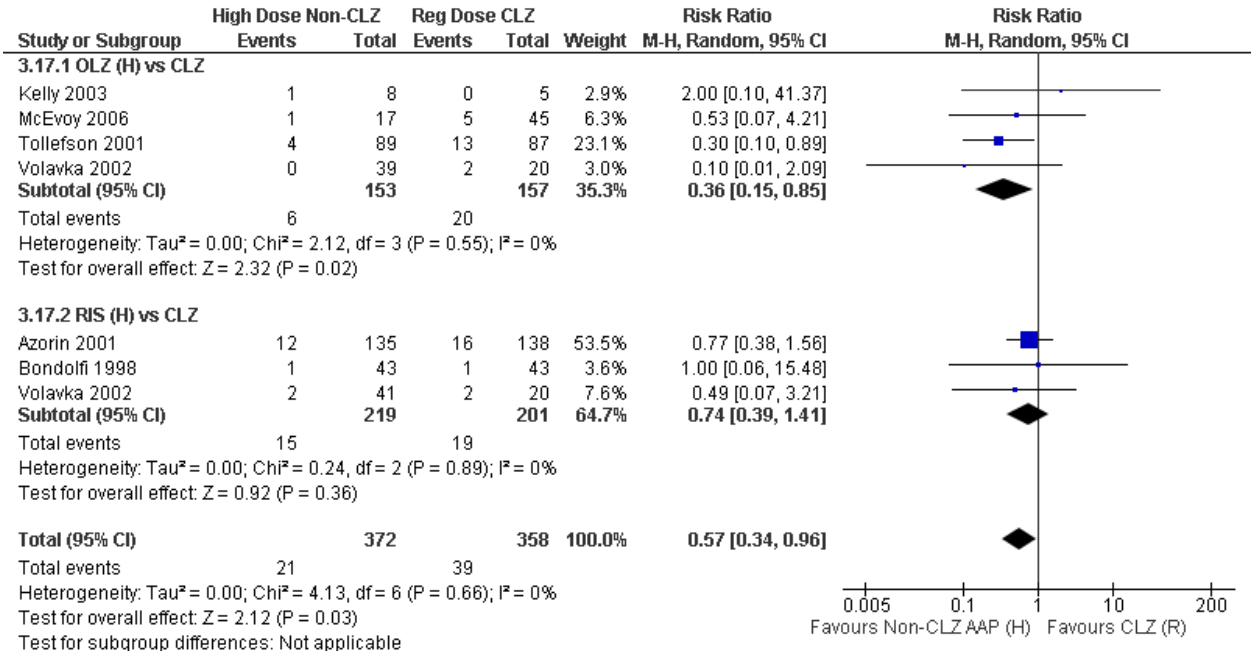



Figure A3.18: Forest plot for high dose non-CLZ AAP versus std dose CLZ: All-cause withdrawals (RR (95% CI)) — reference case

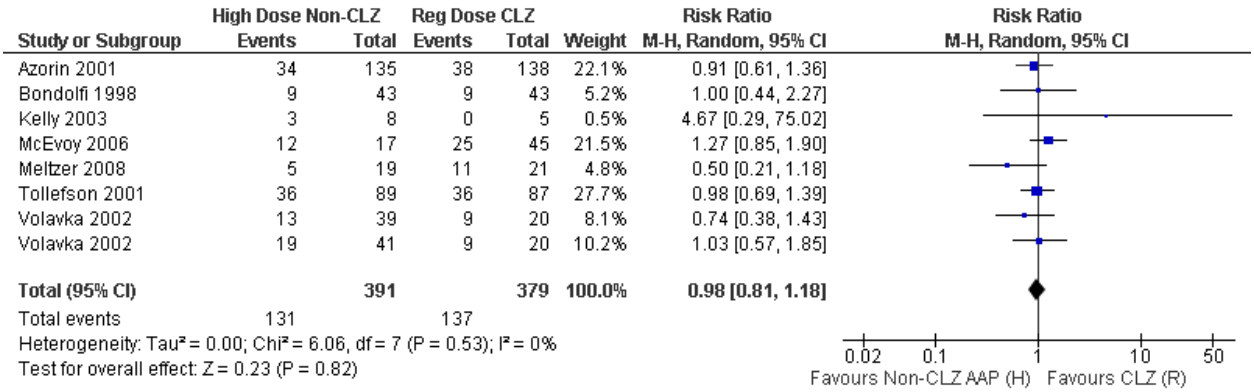


Figure A3.19: Forest plot for high dose non-CLZ AAP versus std dose CLZ: All-cause withdrawals (RR (95% CI)) — subgroup by drug

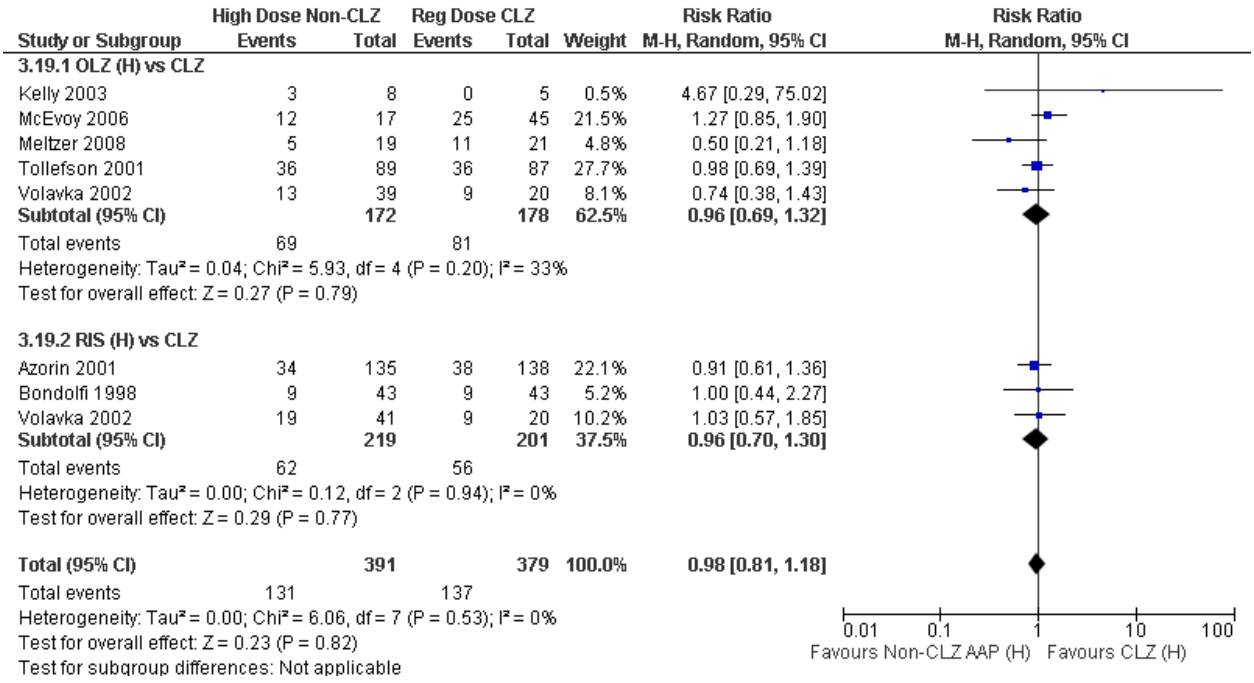



Figure A3.20: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Extrapyramidal effects/disorders (no. of pts) (RR (95% CI)) — reference case

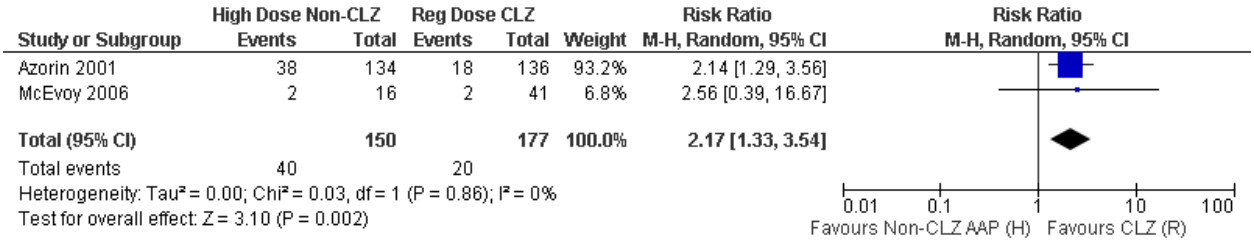


Figure A3.21: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Extrapyramidal effects/disorders (no. of pts) (RR (95% CI)) — subgroup by drug

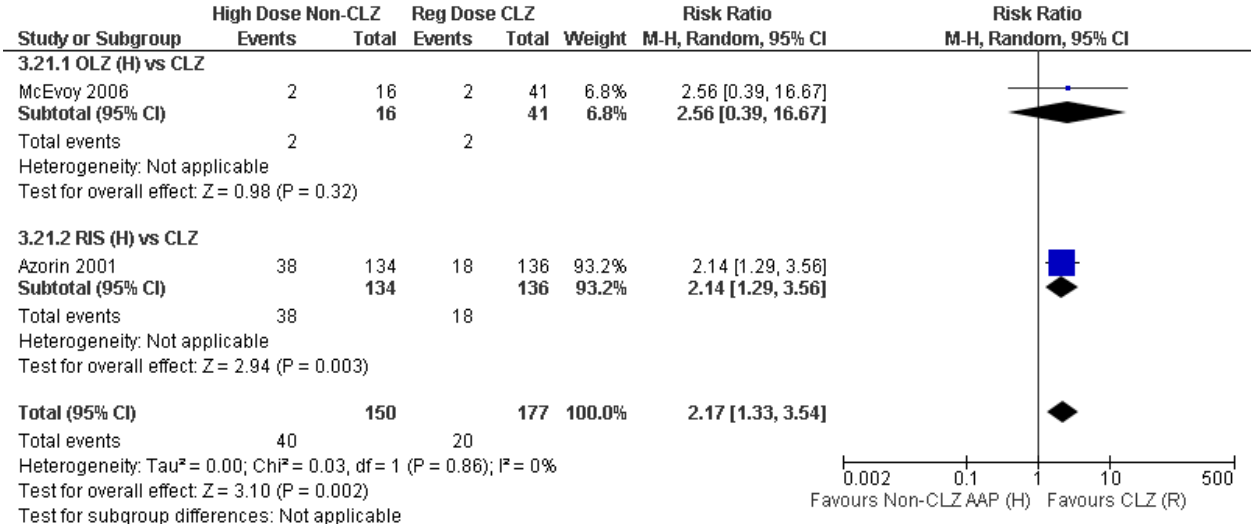



Figure A3.22: Forest plot for high dose non-CLZ AAP versus std dose CLZ: EPS (ESRS) (WMD of changes from baseline (95% CI))

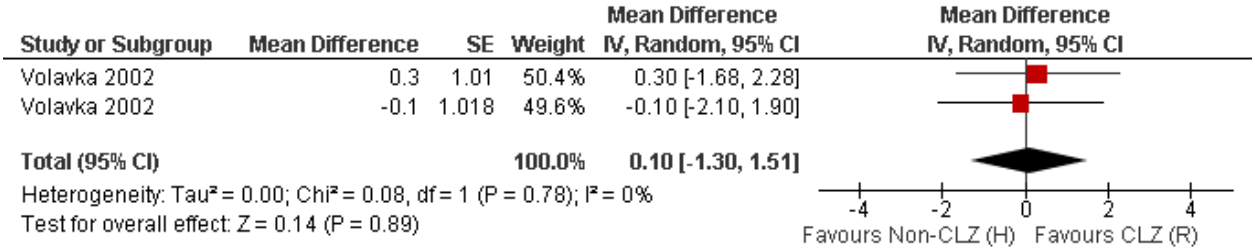



Figure A3.23: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Parkinsonism (RR (95% CI)) — reference case

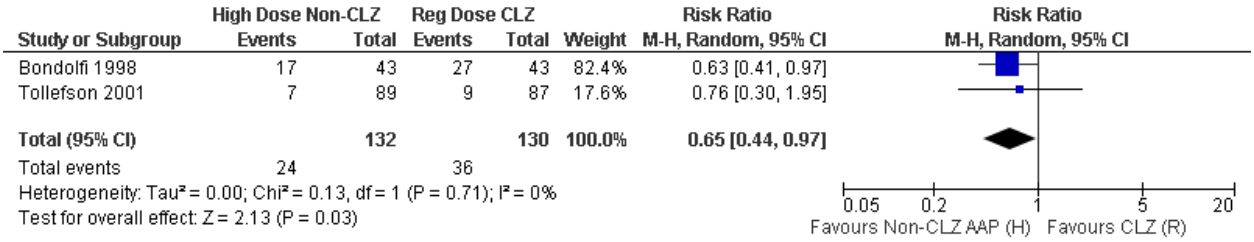


Figure A3.24: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Parkinsonism (RR (95% CI)) — subgroup by drug

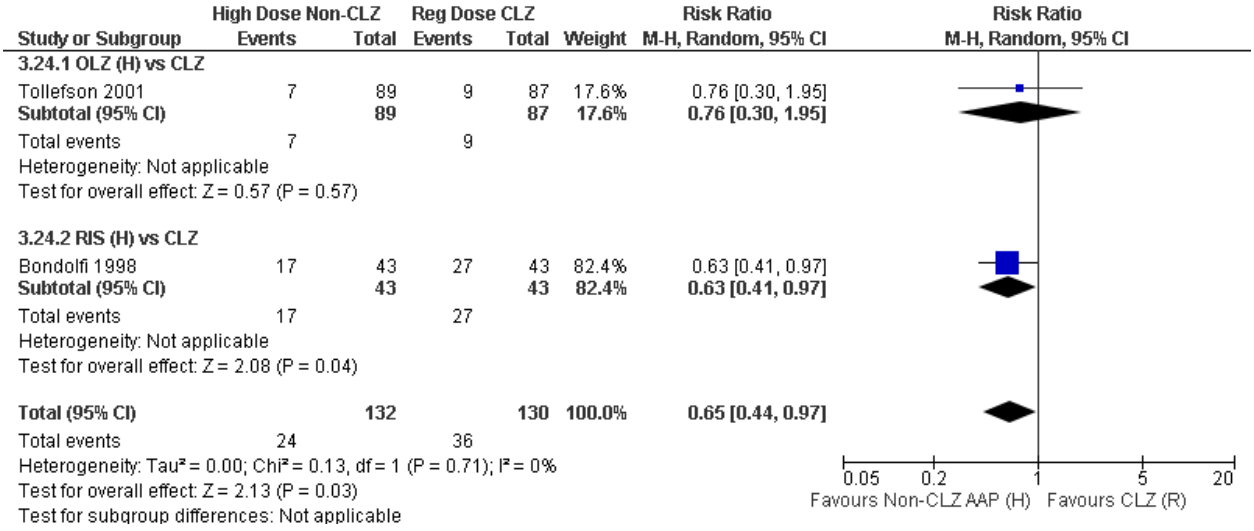



Figure A3.25: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Tardive dyskinesia (RR (95% CI)) — reference case

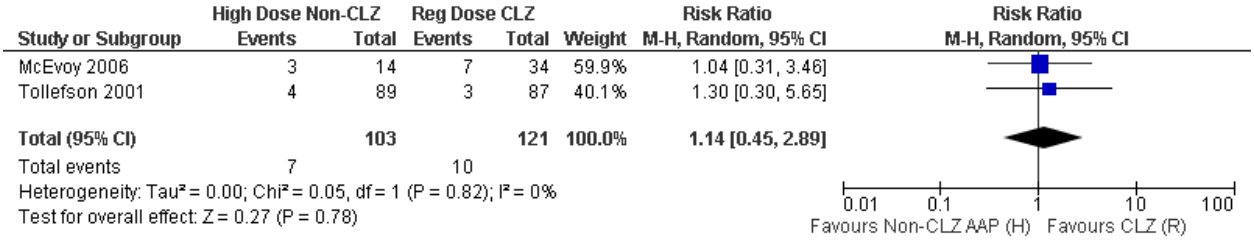



Figure A3.26: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Body weight (kg) (WMD of changes from baseline (95% CI)) — reference case

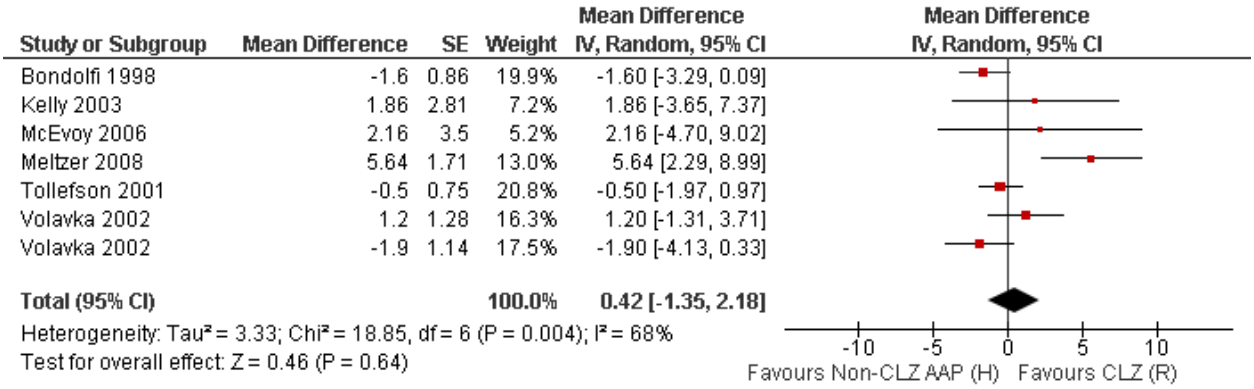


Figure A3.27: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Body weight (kg) (WMD of changes from baseline (95% CI)) — subgroup by drug

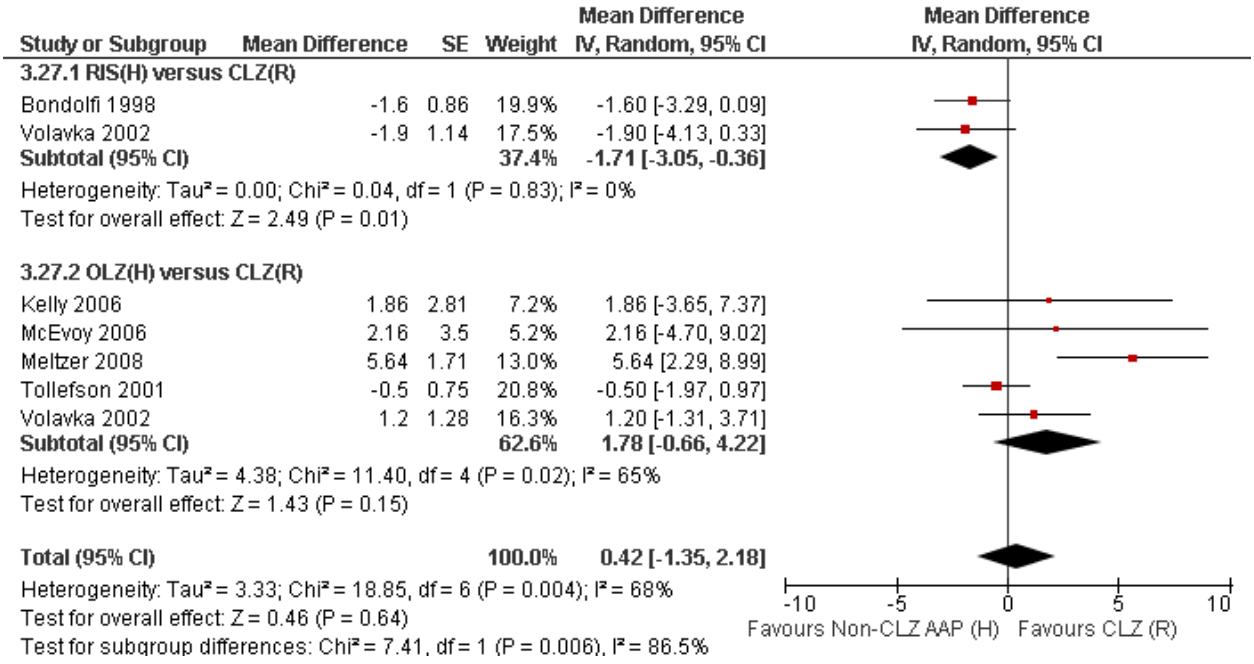



Figure A3.28: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Weight gain (no. of pts) (RR (95% CI)) — reference case

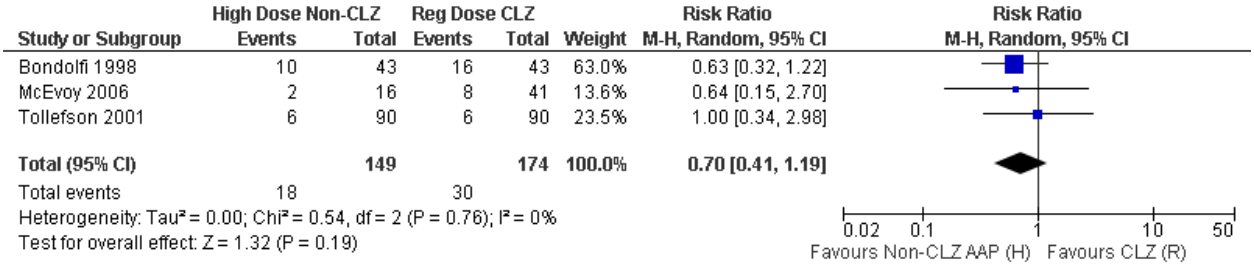


Figure A3.29: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Weight gain (no. of pts) (RR (95% CI)) — subgroup by drug

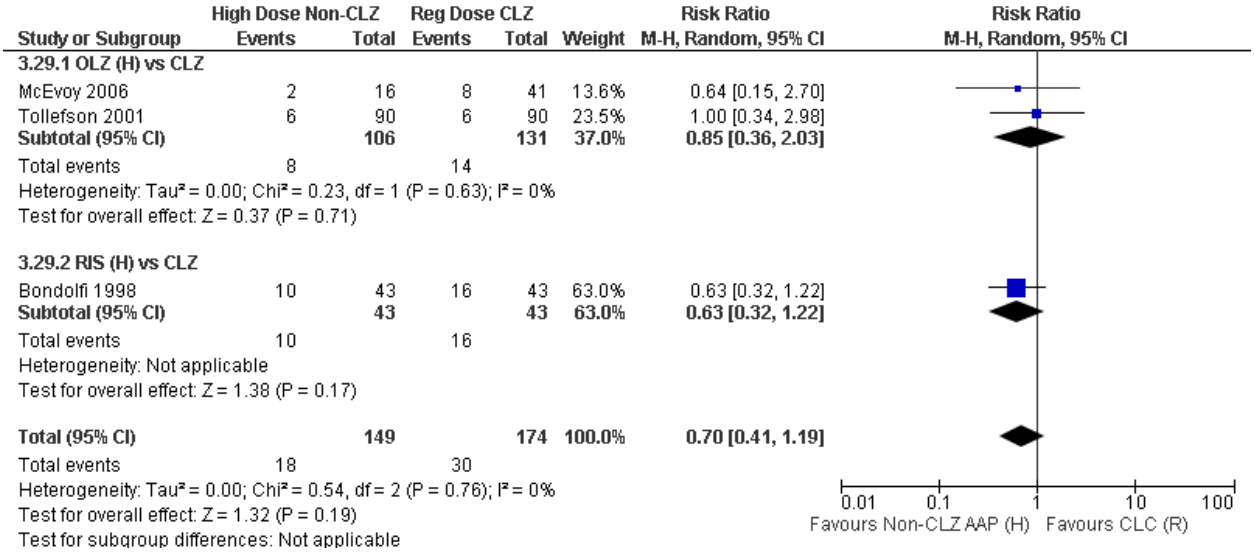



Figure A3.30: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Total cholesterol (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

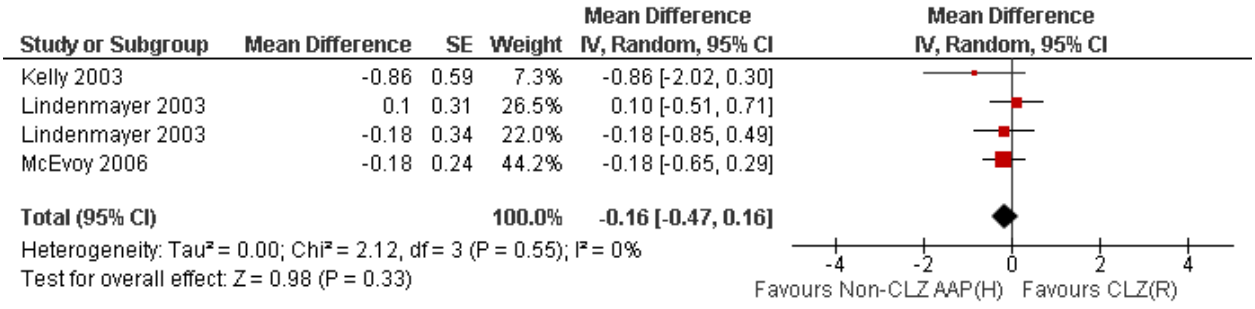



Figure A3.31: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Triglycerides (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

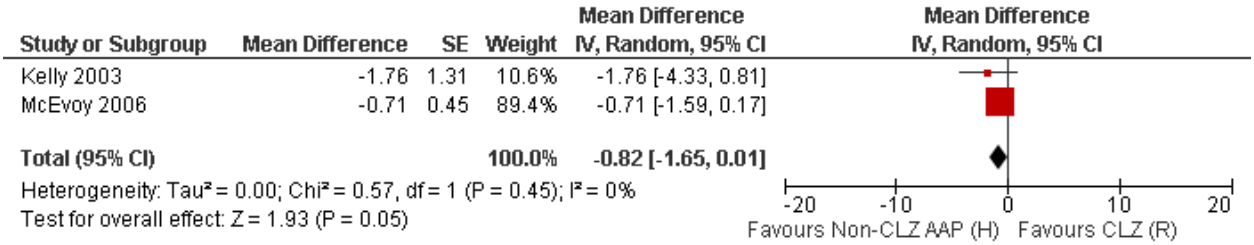


Figure A3.32: Forest plot for high dose non-CLZ AAP versus std dose CLZ: FPG (mmol/L) (WMD of changes from baseline (95% CI)) — reference case

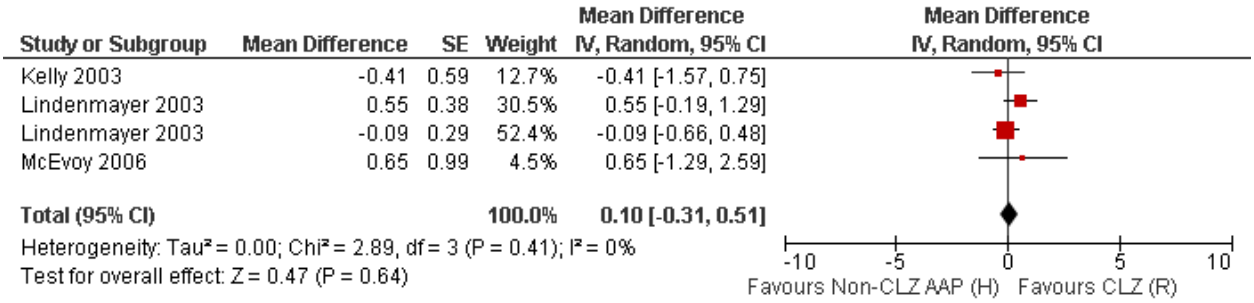



Figure A3.33: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Hyperglycemia (RR (95% CI)) — reference case

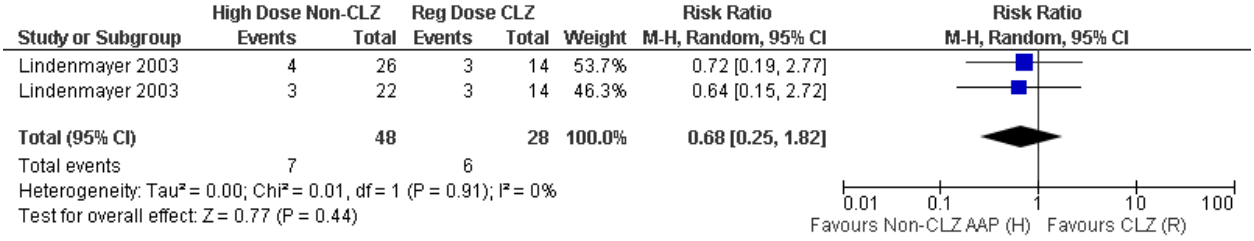



Figure A3.34: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Prolactin (ng/mL) (WMD of changes from baseline (95% CI)) — reference case

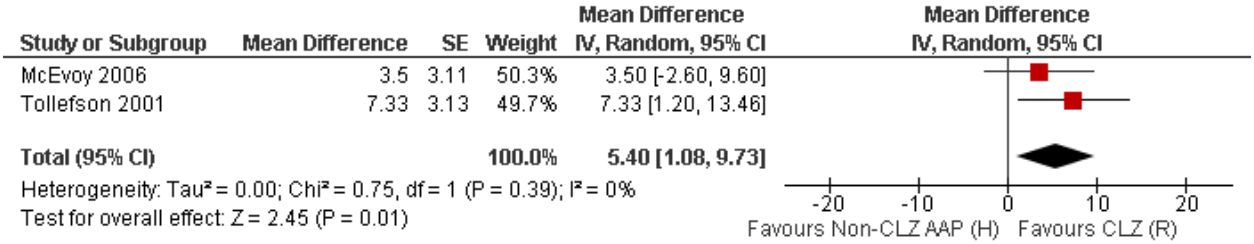
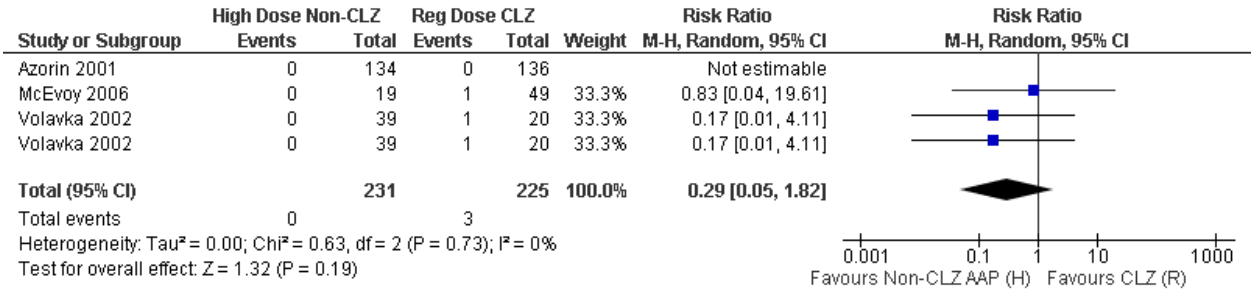
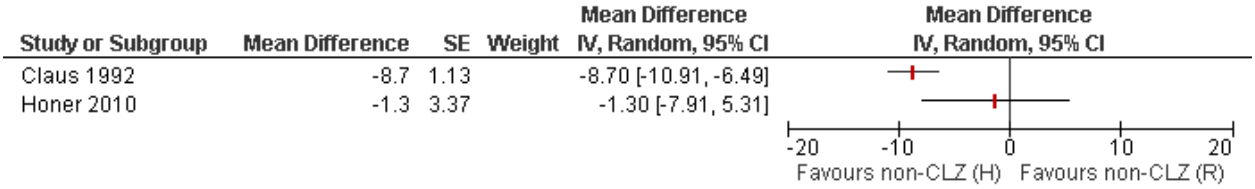



Figure A3.35: Forest plot for high dose non-CLZ AAP versus std dose CLZ: Agranulocytosis (RR (95% CI)) — reference case



## 4. High-Dose Non-CLZ AAP versus Standard-Dose Non-CLZ APD (Figures A4.1 – A4.19)

Figure A4.1: High dose non-CLZ AAP versus non-CLZ APD: PANSS-T (WMD of changes from baseline (95% CI)) — reference case




Results not pooled due to high heterogeneity.

Figure A4.2: High dose non-CLZ AAP versus non-CLZ APD: PANSS-T (WMD of changes from baseline (95% CI)) — subgroup by drug

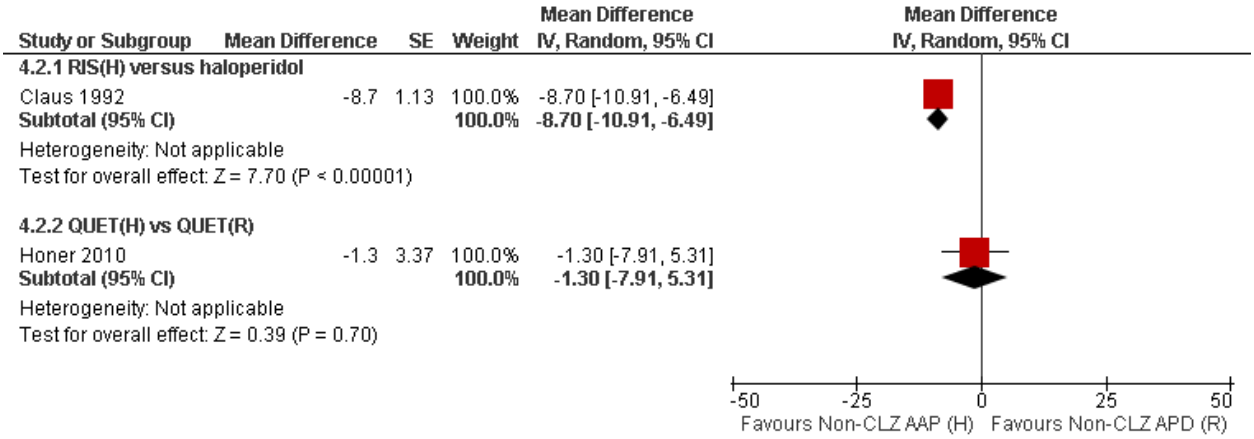
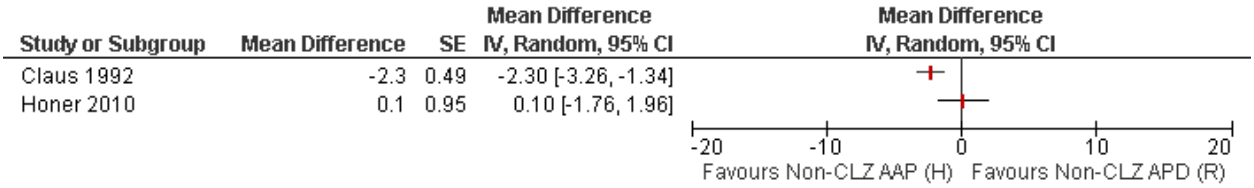



Figure A4.3: High-dose non-CLZ AAP versus non-CLZ APD: PANSS-P (WMD of changes from baseline (95% CI)) — reference case *




*Results not pooled due to high heterogeneity.

Figure A4.4: High dose non-CLZ AAP versus non-CLZ APD: PANSS-P (WMD of changes from baseline (95% CI)) — subgroup by drug

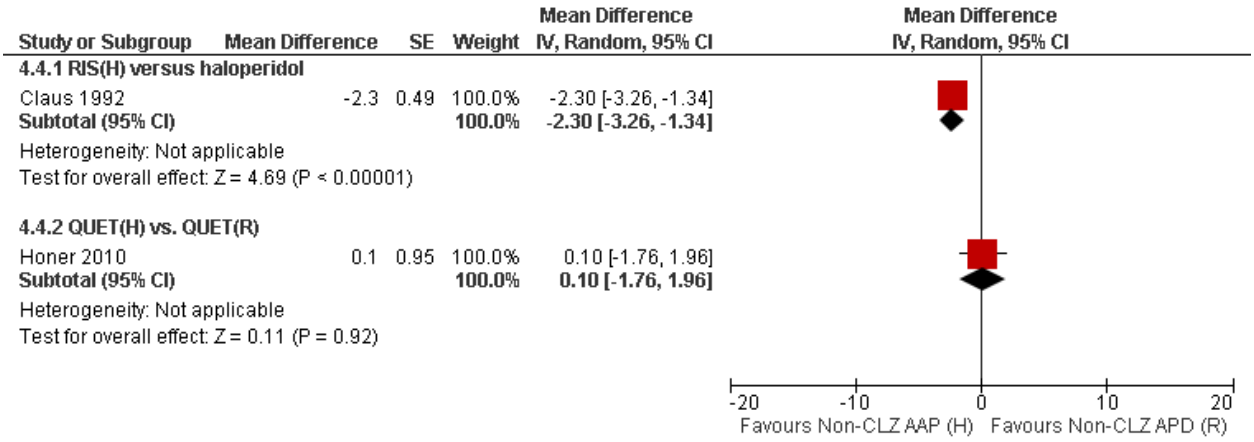



Figure A4.5: High dose non-CLZ AAP versus non-CLZ APD: PANSS-N (WMD of changes from baseline (95% CI)) — reference case

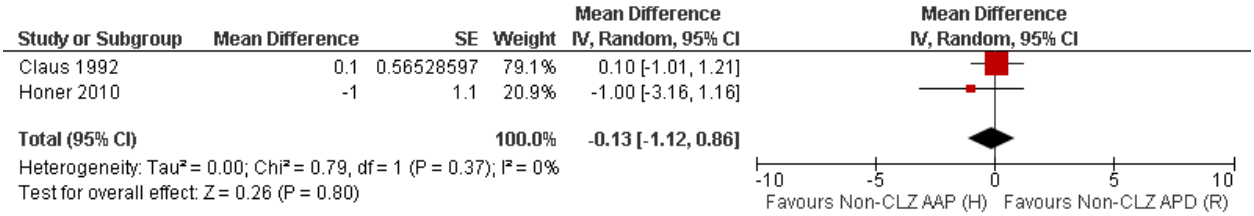



Figure A4.6: High dose non-CLZ AAP versus non-CLZ APD: PANSS-N (WMD of changes from baseline (95% CI)) — subgroup by drug

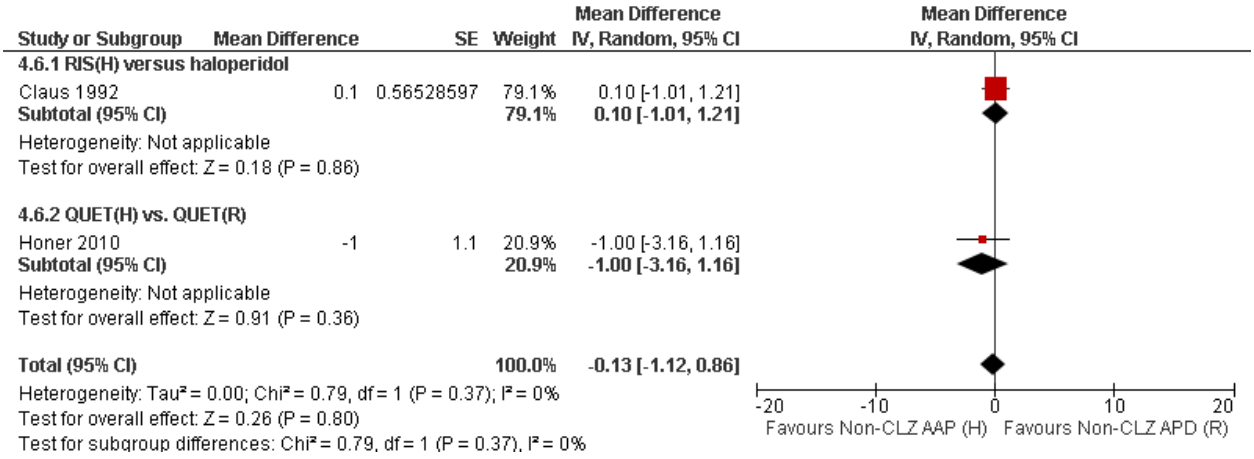


Figure A4.7: High dose non-CLZ AAP versus non-CLZ APD: Response rate (RR (95% CI)) — reference case

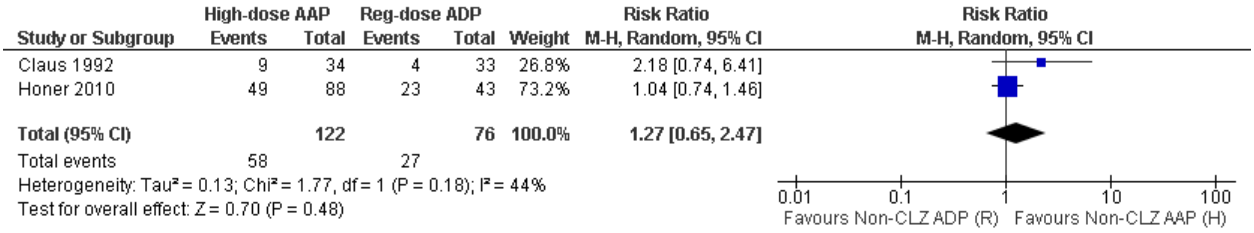



Figure A4.8: High dose non-CLZ AAP versus non-CLZ APD: Response rate (RR (95% CI)) — subgroup by drug

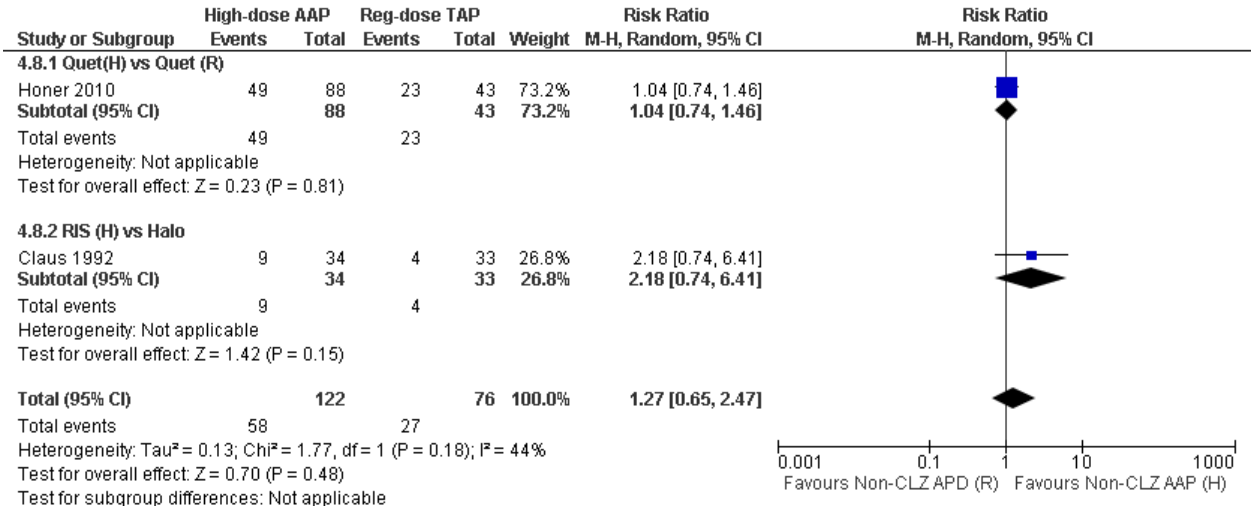



Figure A4.9: High dose non-CLZ AAP versus non-CLZ APD: Persistence with therapy (RR (95% CI)) — reference case

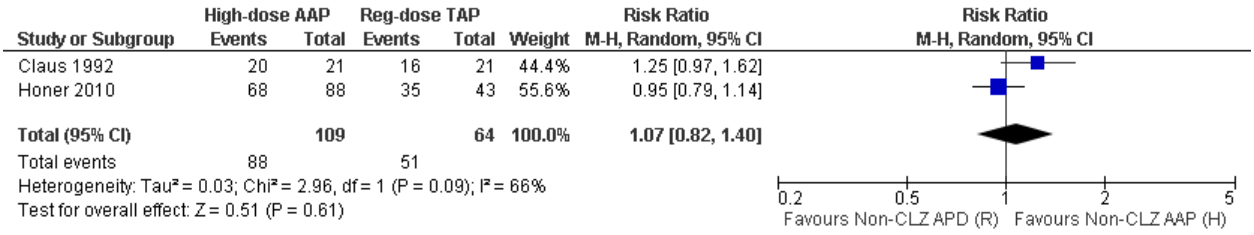


Figure A4.10: High dose non-CLZ AAP versus non-CLZ APD: Persistence with therapy (RR (95% CI)) — subgroup by drug

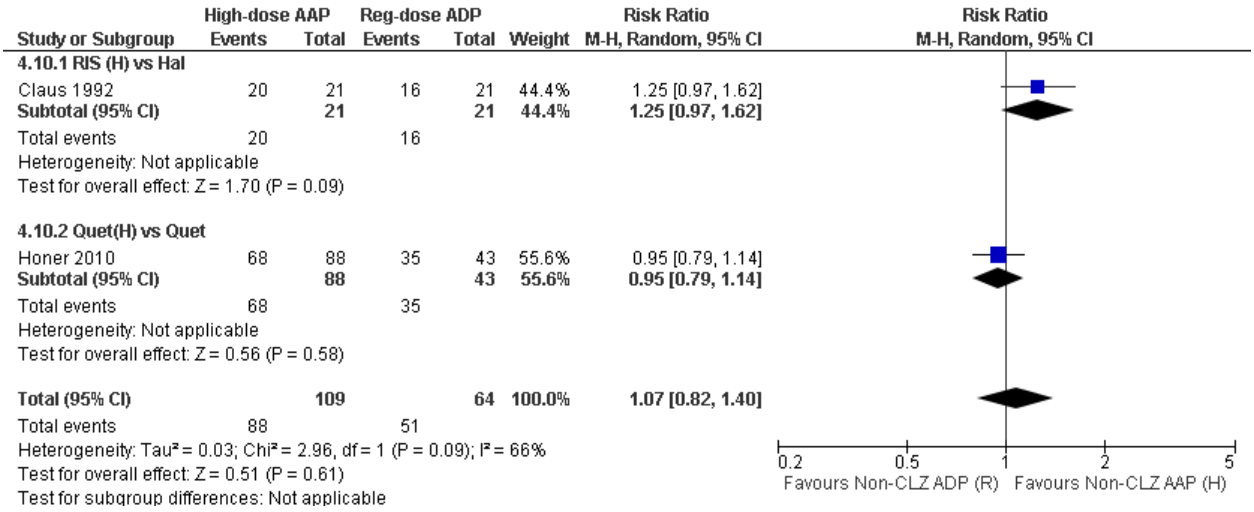



Figure A4.11: High dose non-CLZ AAP versus non-CLZ APD: Withdrawals due to AEs (RR (95% CI)) — reference case

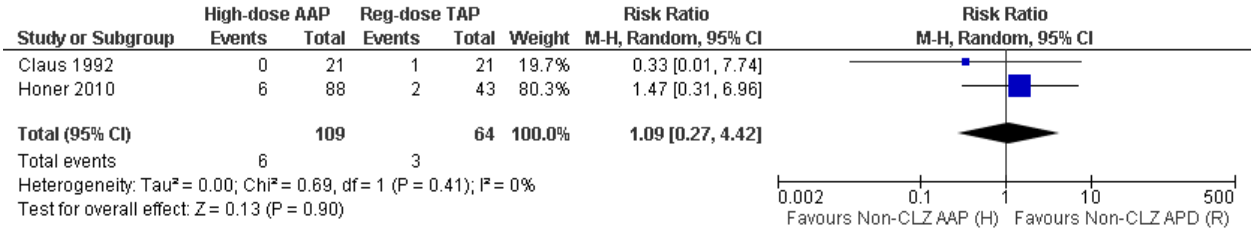



Figure A4.12: High dose non-CLZ AAP versus non-CLZ APD: Withdrawals due to AEs (RR (95% CI)) — subgroup by drug

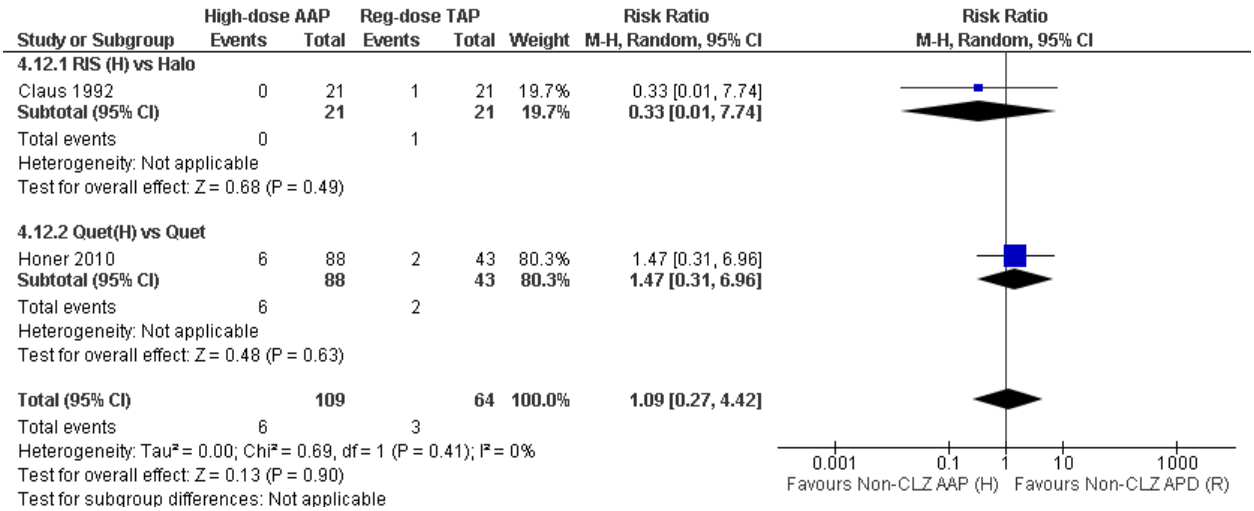


Figure A4.13: High dose non-CLZ AAP versus non-CLZ APD: All-cause withdrawals (RR (95% CI)) — reference case

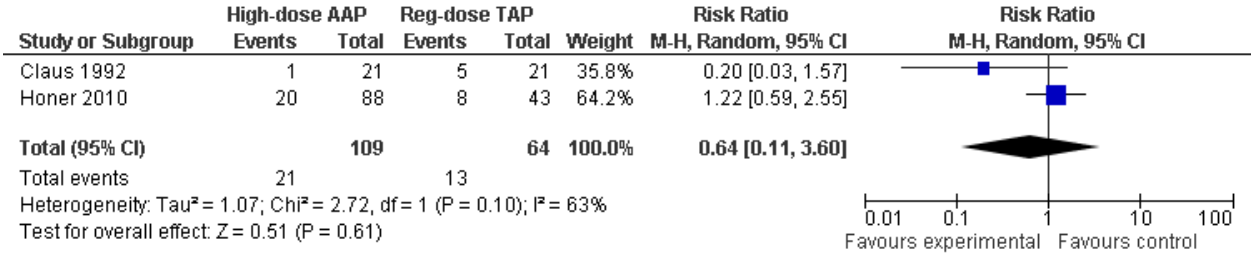



Figure A4.14: High dose non-CLZ AAP versus non-CLZ APD: All-cause withdrawals (RR (95% CI)) — subgroup by drug

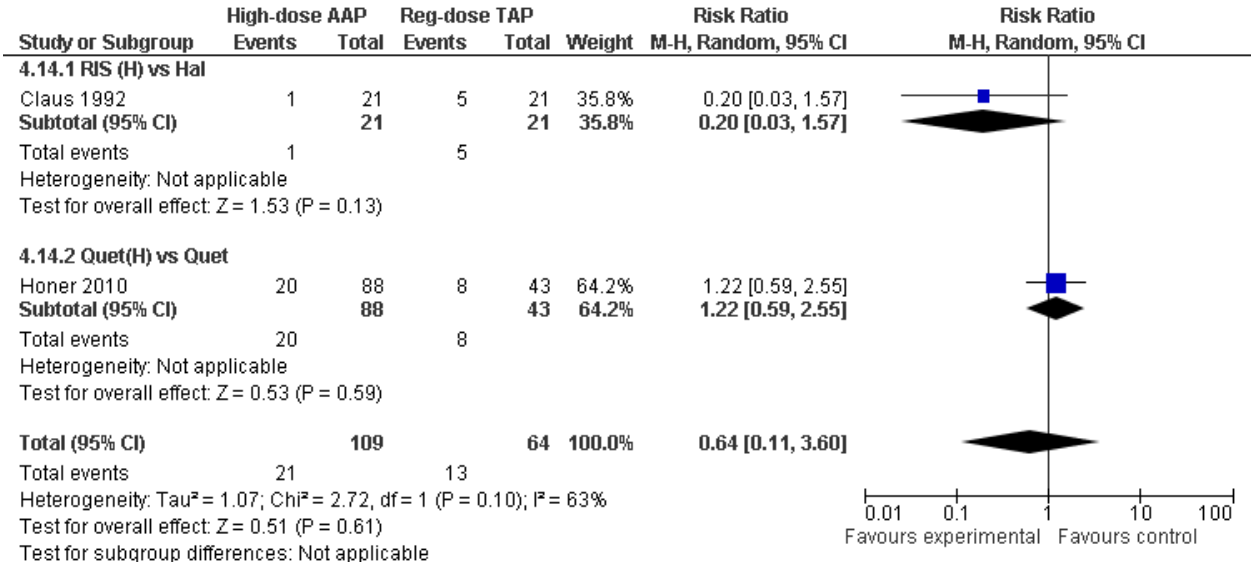



Figure A4.15: High dose non-CLZ AAP versus non-CLZ APD: Extrapyramidal effects/disorders (RR (95% CI)) — reference case

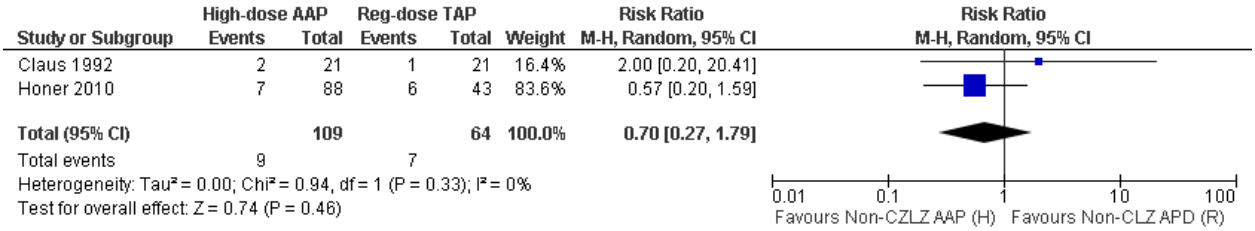


Figure A4.16: High dose non-CLZ AAP versus non-CLZ APD: Extrapyramidal effects/disorders (RR (95% CI)) — subgroup by drug

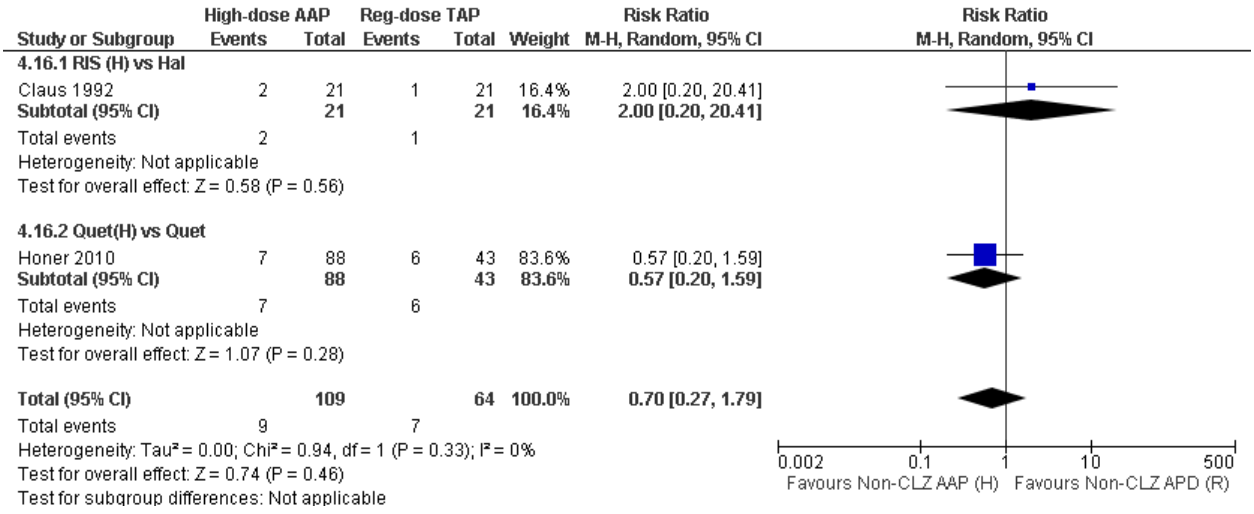



Figure A4.17: High dose non-CLZ AAP versus non-CLZ APD: Body weight (kg) (WMD of changes from baseline (95% CI)) — reference case

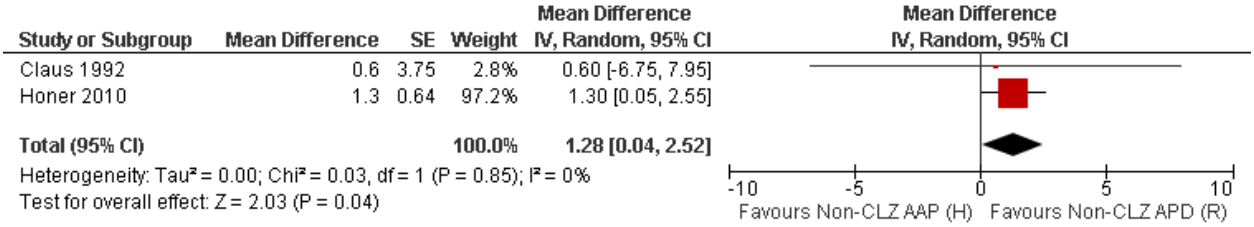



Figure A4.18: High dose non-CLZ AAP versus non-CLZ APD: Body weight (kg) (WMD of changes from baseline (95% CI)) — subgroup by drug

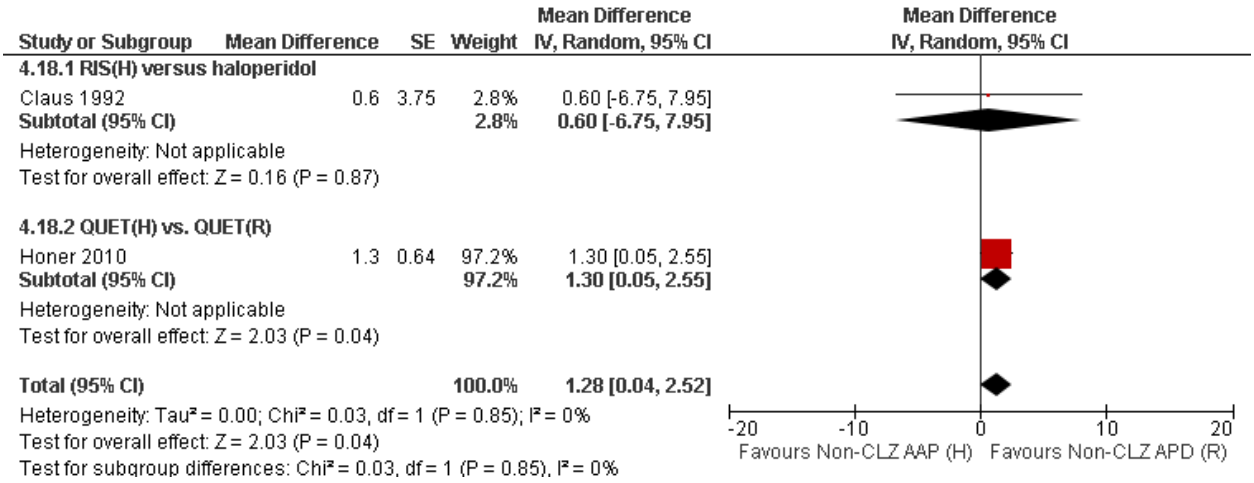
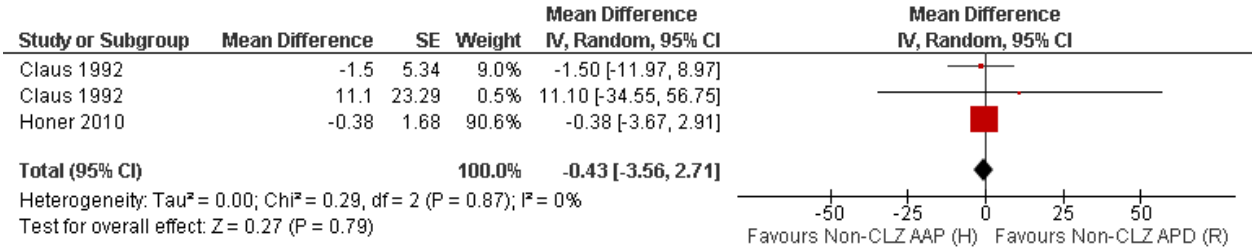


Figure A4.19: High dose non-CLZ AAP versus non-CLZ APD: Prolactin (ng/mL) (WMD of changes from baseline (95% CI)) — reference case



# APPENDIX 5: RESULTS OF SUBGROUP AND SENSITIVITY ANALYSES

**Table A1: CLZ Combination Therapy versus CLZ Monotherapy**

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| **Efficacy Outcomes** | | | | | | | | | | |
| **PANSS-T** | Not pooled* | (RIS+CLZ) vs. (PL+CLZ) | Not pooled* | **1 or more** | N/A | N/A | Not pooled* | Not pooled* | N/A | N/A |
| | | (ARI+CLZ) vs. (PL+CLZ) | -1.10 (-3.61, 1.41) | **2 or more** | Not pooled* | | | | | |
| | | | | **3 or more** | 5.70 (0.96, 10.44) | | | | | |
| | | | | **No. of APD -NR** | -1.10 (-3.61, 1.41) | | | | | |
| **PANSS-P** | 0.23 (-0.97, 1.43) | (RIS+CLZ) vs. (PL+CLZ) | Not pooled* | **1 or more** | N/A | N/A | N/A | Not pooled* | N/A | N/A |
| | | (ARI+CLZ) vs. (PL+CLZ) | -0.50 (-1.15, 0.15) | **2 or more** | -0.39 (-1.26, 0.48) | | | | | |
| | | | | **3 or more** | 2.40 (0.87, | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| | | | | | 3.93) | | | | | |
| | | | | No. of APD-NR | -0.50 (-1.15, 0.15) | | | | | |
| **PANSS-N** | -0.34 (-1.07, 0.39) | (RIS+CLZ) vs. (PL+CLZ) | -0.15 (-1.44, 1.15) | **1 or more** | N/A | N/A | N/A | -0.25 (-1.90, 1.41) | N/A | N/A |
| | | (ARI+CLZ) vs. (PL+CLZ) | -0.40 (-1.30, 0.50) | **2 or more** | -0.79 (-1.85, 0.27) | | | | | |
| | | | | **3 or more** | 0.70 (-0.79, 2.19) | | | | | |
| | | | | **No. of APD-NR** | -0.40 (-1.30, 0.50) | | | | | |
| **BPRS** | -0.88 (-4.32, 2.55) | (RIS+CLZ) vs. (PL+CLZ) | -3.10 (-7.20, 1.00) | **1 or more** | Not pooled* | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+CLZ) vs. (PL+CLZ) | 0.50 (-1.79, 2.79) | **2 or more** | N/A | | | | | |
| | | | | **3 or more** | 0.50 (-1.79, 2.79) | | | | | |
| | | | | **No. of** | N/A | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| | | | | APD-NR | | | | | | |
| **CGI-I** | -0.30 (-0.58, -0.02) (WMD btw groups at the endpoint) | NA | | | | | | | | |
| **CGI-S** | 0.04 (-0.22, 0.30) | (RIS+CLZ) vs. (CLZ) | -0.10 (-0.39, 0.19) | **1 or more** | -0.20 (-0.61, 0.21) | -0.11 (-0.26, 0.03) | N/A | N/A | 0.04 (-0.22, 0.30) | N/A |
| | | (ARI+CLZ) vs. (CLZ) | Not pooled* | **2 or more** | -0.02 (-0.45, 0.41) | | | | | |
| | | | | **3 or more** | 0.40 (0.13, 0.67) | | | | | |
| | | | | **No. of APD-NR** | -0.10 (-0.26, 0.06) | | | | | |
| **GAF** | -1.43 (-6.28, 3.42) | (RIS+CLZ) vs. (CLZ) | -4.60 (-9.99, 0.79) | **1 or more** | N/A | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+CLZ) vs. (CLZ) | 0.50 (-1.70, 2.70) | **2 or more** | N/A | | | | | |
| | | | | **3 or more** | -4.60 (-9.99, 0.79) | | | | | |
| | | | | **No. of** | 0.50 (-1.70, | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| | | | | **APD-NR** | 2.70) | | | | | |
| **Response Rate** | 1.35 (0.81, 2.25) | (RIS+CLZ) vs. (PI+CLZ) | 1.16 (0.61, 2.21) | **1 or more** | 1.09 (0.30, 4.01) | 1.23 (0.58, 2.62) | N/A | 1.66 (0.31, 8.90) | 1.21 (0.71, 2.05) | N/A |
| | | (ARI+CLZ) vs. (PI+CLZ) | 1.31 (0.52, 3.31) | **2 or more** | 1.60 (0.68, 3.74) | | | | | |
| | | (SUL+CLZ) vs. (PI+CLZ) | 6.00 (0.86, 41.73) | **3 or more** | Not pooled* | | | | | |
| | | | | **No. of APD-NR** | 1.31 (0.52, 3.31) | | | | | |
| **Persistence with therapy** | 0.97 (0.92, 1.02) | (RIS+CLZ) vs. (PI+CLZ) | 0.96 (0.88, 1.04) | **1 or more** | N/A | 0.96 (0.89, 1.03) | 0.97 (0.93, 1.02) | 0.97 (0.87, 1.08) | 0.96 (0.91, 1.02) | 0.97 (0.92, 1.02) |
| | | (ARI+CLZ) vs. (PI+CLZ) | 0.96 (0.89, 1.03) | **2 ore more** | N/A | | | | | |
| | | (AMI+CLZ) vs. (PI+CLZ) | 1.27 (0.55, 2.92) | **3 or more** | N/A | | | | | |
| | | (SUL+CLZ) | 1.00 (0.87, | **# of APD-** | N/A | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| | | vs. (PI+CLZ) | 1.15) | NR | | | | | | |
| **QOL** | **0.30(-5.93, 6.53)** | **N/A** | | | | | | | | |
| **Adverse Events** | | | | | | | | | | |
| **SAEs** | 8.45 (1.03, 69.54) | (RIS+CLZ) | 3.00 (0.13, 71.15) | | | N/A | N/A | N/A | 8.45 (1.03, 69.54) | 8.45 (1.03, 69.54) |
| | | (ARI+CLZ) | 19.27 (1.14, 324.53) | | | | | | | |
| | | (AMI+CLZ) | Not estimable | | | | | | | |
| | | (SUL+CLZ) | Not estimable | | | | | | | |
| **WDAES** | 1.68 (0.49, 5.75) | (RIS+CLZ) vs. (PI+CLZ) | 3.00 (0.13, 71.15) | | | N/A | N/A | N/A | 1.68 (0.49, 5.75) | 1.68 (0.49, 5.75) |
| | | (ARI+CLZ) vs. (PI+CLZ) | 1.65 (0.27, 10.02) | | | | | | | |
| | | (AMI+CLZ | Not | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| | | ) vs. (PI+CLZ) | estimable | | | | | | | |
| | | (SUL+CLZ) vs. (PI+CLZ) | Not estimable | | | | | | | |
| **All-Cause withdrawal** | 1.30 (0.78, 2.17) | (RIS+CLZ) vs. (PI+CLZ) | 1.32 (0.66, 2.67) | | | 1.32 (0.70, 2.51) | 1.15 (0.73, 1.82) | 1.93 (0.46, 8.00) | 1.39 (0.82, 2.37) | 1.39 (0.82, 2.37) |
| | | (ARI+CLZ) vs. (PI+CLZ) | 1.49 (0.66, 3.35) | | | | | | | |
| | | (AMI+CLZ) vs. (PI+CLZ) | 0.46 (0.06, 3.57) | | | | | | | |
| | | (SUL+CLZ) vs. (PI+CLZ) | Not estimable | | | | | | | |
| **Hospitalization** | 3.00 (0.13, 71.15) | N/A | | | | | | | | |
| **Mortality** | Not estimable | **N/A** | | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| **Adverse Events — EPS-Related** | | | | | | | | | | |
| **Akathisia** | 3.41 (0.46, 25.44) | (RIS+CLZ) vs. (PI+CLZ) | Not estimable | | | N/A | N/A | N/A | N/A | 6.30 (0.33, 120.45) |
| | | (ARI+CLZ) vs. (PI+CLZ) | 6.30 (0.33, 120.45) | | | | | | | |
| | | AMI+CLZ) vs. (PI+CLZ) | 2.00 (0.13, 31.19) | | | | | | | |
| | | (SUL+CLZ) vs. (PI+CLZ) | Not estimable | | | | | | | |
| **EPS (number of patients)** | 2.25 (0.73, 6.94) | N/A | | | | | | | | |
| **EPS score (ESRS-T, DIEPSS)** | 0.18 (-0.77, 1.13) | N/A | | | | | | | | |
| **Parkinson** | 0.60 (0.08, | N/A | | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| **ism** | 4.54) | | | | | | | | | |
| **Tardive Dyskinesia** | Not estimable | N/A | | | | | | | | |
| **AIMS** | 0.02 (-0.77. 0.80) | N/A | | | | N/A | N/A | -0.19 (-1.62, 1.25) | N/A | N/A |
| **BA(R)S** | -0.29 (-0.79, 0.20) | N/A | | | | N/A | N/A | -0.24 (-0.87, 0.40) | N/A | N/A |
| **SA(R)S** | -0.25 (-0.72, 0.22) | (RIS+CLZ) vs. (PI+CLZ) | -0.61 (-1.32, 0.10) | | | -0.04 (-0.44, 0.36) | N/A | -1.00 (-1.94, -0.05) | N/A | N/A |
| | | (ARI+CLZ) vs. (PI+CLZ) | -0.03 (-0.46, 0.40) | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| **Adverse Events — Body weight** | | | | | | | | | | |
| **Body Weight (kg)** | Not pooled * | (RIS+CLZ) vs. (PL+CLZ) | 0.21 (-0.80, 1.23) | | | -1.92 (-2.84, -1.01) | N/A | N/A | N/A | N/A |
| | | (ARI+CLZ) vs. (PL+CLZ) | Not pooled * | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **Weight gain (# of pts)** | 0.65 (0.16, 2.61) | (RIS+CLZ) vs. (PI+CLZ) | 0.45 (0.06, 3.33) | | | 0.58 (0.11, 2.97) | N/A | N/A | N/A | N/A |
| | | (ARI+CLZ) vs. (PI+CLZ) | 0.92 (0.13, 6.38) | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **Adverse Effects — Metabolic and Other Laboratory Parameters** | | | | | | | | | | |
| **Total Cholester** | -0.15 | (RIS+CLZ) vs. (PI+CLZ) | -0.15 (-0.25, -0.05) | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| **ol (mmol/L)** | (-0.25, -0.06) | (ARI+CLZ) vs. (PI+CLZ) | -0.19 (-0.46, 0.09) | | | N/A | N/A | N/A | N/A | N/A |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **HDL (mmol/L)** | -0.01 (-0.08, 0.06) | (RIS+CLZ) vs. (PI+CLZ) | -0.08 (-0.27, 0.11) | | | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+CLZ) vs. PI+CLZ) | 0.00 (-0.08, 0.09) | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **LDL (mmol/L)** | -0.20 (-0.34, -0.07) | (RIS+CLZ) vs. (PI+CLZ) | 0.04 (-0.43, 0.51) | | | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+CLZ) vs. (PI+CLZ) | -0.23 (-0.36, -0.10) | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| **Triglycerides (mmol/L)** | -0.21 (-0.60, 0.17) | (RIS+CLZ) vs. (PI+CLZ) | 0.02 (-0.74, 0.78) | | | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+CLZ) vs. (PI+CLZ) | Not pooled * | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **FPG (mmol/L)** | -0.12 (-0.54, 0.31) | (RIS+CLZ) vs. (PI+CLZ) | 0.10 (-1.20, 1.40) | | | -0.08 (-0.35, 0.20) | N/A | N/A | N/A | N/A |
| **Hyperglycemia** | 1.50 (0.48, 4.68) | N/A | | | | | | | | |
| **Agranulocytosis** | Not estimable | N/A | | | | | | | | |
| **Prolactin (ng/mL)** | Not pooled * | (RIS+CLZ) vs. (PI+CLZ) | Not pooled * | | | N/A | N/A | 53.34 (35.55, 71.13) | N/A | N/A |
| | | (ARI+CLZ) vs. (PI+CLZ) | 11.65 (-23.34, 46.64) | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drug/ strategy | WMD or RR (95% CI) | No. failed | WMD or RR (95% CI) | | | | | |
| | | (SUL+CLZ) vs. (PI+CLZ) | 62.77 (37.17, 88.38) | | | | | | | |
| | | | | | | | | | | |

* Data not pooled due to $I^2$>75%

**Table A2: Non-CLZ Combinations versus Non-CLZ Monotherapy**

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/ d removed |
| | | Drugs/st rategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **Efficacy Outcomes** | | | | | | | | | | |
| **PANSS-T** | -0.10 (-2.59, 2.79) | N/A | | | | N/A | | | | |
| **PANSS-P** | 0.50 (-0.40, 1.40) | | | | | | | | | |
| **PANSS-N** | 0.10 (-0.84, 1.04) | | | | | | | | | |
| **CGI-I** | -0.10 (-0.38, 0.18) (WMD btw groups at the endpoint) | | | | | | | | | |
| **CGI-S** | 0.00 (-0.19, 0.19) | | | | | | | | | |
| **Response Rate** | 1.01 (0.78, 1.33) | | | | | | | | | |
| **Persistence with therapy** | 0.99 (0.86, 1.15) | (ARI+RIS) vs. (RIS) | 1.05 (0.86, 1.28) | **1 or more** | N/A | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+QUET) vs. | 0.93 (0.75, 1.15) | **2 or more** | N/A | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| | | (QUET) | | | | | | | | |
| **Quality of Life** | -1.10 (-4.06, 1.86) | N/A | | | | N/A | | | | |
| **Adverse Events** | | | | | | | | | | |
| **SAEs** | 0.38 (0.17, 0.85) | N/A | | | | | | | | |
| **WDAEs** | 0.51 (0.23, 1.12) | | | | | | | | | |
| **All-cause WD** | 1.02 (0.74, 1.41) | (ARI+RIS) vs. (RIS) | 0.90 (0.58, 1.39) | **1 or more** | N/A | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+QUET) vs. (QUET) | 1.19 (0.73, 1.96) | **2 or more** | N/A | | | | | |
| | | | | **3 or more** | N/A | | | | | |
| | | | | **# of APD-NR** | N/A | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/ d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **Suicidal Ideation** | 0.08 (0.00, 1.48) | | | | | | | | | |
| **Suicide Attempted** | 0.30 (0.01, 7.36) | | | | | | | | | |
| **Suicide Completed** | Not estimable | | | | | | | | | |
| **Mortality All-cause** | Not estimable | | | | | | | | | |
| **Adverse Events — EPS-Related** | | | | | | | | | | |
| **Akathisia** | 0.82 (0.36, 1.88) | | | | | | | | | |
| **EPS (no. of pts)** | 0.67, (0.35, 1.28) | | | | | | | | | |
| **Adverse Events — Body Weight** | | | | | | | | | | |
| **Weight (kg)** | 0.20 (-0.92, 1.32) | | | | | | | | | |
| **Weight gain (# of pts.)** | 1.41 (0.77, 2.61) | | | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Abstracts added (WMD 95% CI) | Non-ITT removed | Drug not used in Canada removed | CLZ < 350 mg/ d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **Adverse Effects — Metabolic and Other** | | | | | | | | | | |
| **Total Cholesterol (mmol/L)** | -0.05 (-0.13, 0.03) | | | | | | | | | |
| **HDL (mmol/L)** | 0.05 (-0.04, 0.14) | | | | | | | | | |
| **LDL (mmol/L)** | -0.03 (-0.09, 0.04) | | | | | | | | | |
| **Triglyceride(mmol/L)** | -0.21 (-0.60, 0.18) | | | | | | | | | |
| **FPG (mmol/L)** | 0.03 (-0.26, 0.32) | | | | | | | | | |
| **Prolactin (ng/mL)** | -10.40 (-16.53, -4.27) | (ARI+RIS) vs. (PI+RIS) | -16.80 (-26.64, -6.96) | | | N/A | N/A | N/A | N/A | N/A |
| | | (ARI+QUET) vs. (PI+QUET) | -3.16 (-6.94, 0.62) | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

* Data not pooled due to $I^2$>75%

**Table A3: High-Dose Non-CLZ AAP versus Standard-Dose CLZ**

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Adolescent study added | Non-ITT removed | Crossover removed | CLZ < 350 mg/d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **Efficacy Outcomes** | | | | | | | | | | |
| **PANSS-T** | 2.09 (-2.71, 6.90) | RIS(H) vs. CLZ(R) | 3.60 (-4.52, 11.71) | **1 or more** | 6.17 (0.69, 11.66) | 3.00 (-2.14, 8.14) | N/A | -2.56 (-7.05, 1.92) | N/A | 3.10 (-2.69, 8.89) |
| | | OLZ(H) vs. CLZ(R) | 0.84 (-5.31, 7.00) | **2 or more** | -2.56 (-7.05, 1.92) | | | | | |
| **PANSS-P** | 0.93 (-0.40, 2.27) | RIS(H) vs. CLZ(R) | 0.92 (-1.55, 3.38) | **1 or more** | 1.60 (0.11, 3.09) | 1.22 (-0.11, 2.54) | N/A | 0.25 (-2.06, 2.57) | N/A | 1.68 (0.09, 3.28) |
| | | OLZ(H) vs. CLZ(R) | 0.71 (-1.00, 2.43) | **2 or more** | 0.25 (-2.06, 2.57) | | | | | |
| **PANSS-N** | 0.47 (-1.41, 2.34) $I^2$=75% | RIS(H) vs. CLZ(R) | 1.25 (-0.18, 2.68) | **1 or more** | 2.07 (0.21, 3.93) | Not pooled * | N/A | -1.53 (-3.03, -0.03) | N/A | 0.05 (-2.30, 2.39) |
| | | OLZ(H) vs. CLZ(R) | Not pooled * | **2 or more** | -1.53 (-3.03, -0.03) | | | | | |
| **BPRS** | Not pooled* | RIS(H) vs. CLZ(R) | 7.10 (3.65, 10.55) | **1 or more** | 7.10 (3.65, 10.55) | Not pooled* | Not pooled* | N/A | N/A | N/A |
| | | OLZ(H) vs. CLZ(R) | -1.20 (-5.43, 3.03) | **2 or more** | -1.20 (-5.43, 3.03) | | | | | |
| **CGI-I Endpoint diff** | -0.30 2.26, 1.66) | N/A | | **1 or more** | N/A | N/A | 0.68 (-0.53, 1.89) | N/A | N/A | N/A |
| | | | | **2 or more** | N/A | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Adolescent study added | Non-ITT removed | Crossover removed | CLZ < 350 mg/d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **CGI-S** | 0.21 (-0.13, 0.54) | RIS(H) vs. CLZ(R) | 0.40 (0.01, 0.79) | **1 or more** | 0.60 (0.30, 0.90) | Not pooled* | 0.23 (-0.07, 0.53) | 0.01 (-0.26, 0.27) | N/A | 0.34 (-0.24, 0.93) |
| | | OLZ(H) vs. CLZ(R) | -0.02 (-0.39, 0.34) | **2 or more** | 0.01 (-0.26, 0.27) | | | | | |
| **GAF** | -7.50 (-12.83, -2.17) | N/A | | | | | | | | |
| **Response Rate** | 0.97 (0.84, 1.14) | RIS(H) vs. CLZ | 0.92 (0.74, 1.15) | **1 or more** | 0.83 (0.63, 1.10) | 0.95 (0.78, 1.16) | 0.92 (0.76, 1.12) | 1.04 (0.87, 1.26) | N/A | 0.83 (0.65, 1.07) |
| | | OLZ(H) vs. CLZ | 1.05 (0.83, 1.33) | **2 or more** | 1.04 (0.87, 1.26) | | | | | |
| **Persistence with therapy** | 0.95 (0.80, 1.13) | RIS(H) vs. CLZ | 0.88(0.73, 1.05) | **1 or more** | N/A | 0.98 (0.78, 1.24) | 0.94 (0.81, 1.09) | 1.06 (0.88, 1.26) | 0.98 (0.82, 1.17) | 0.97 (0.72, 1.30) |
| | | OLZ(H) vs. CLZ | 1.02 (0.79, 1.33) | **2 or more** | N/A | | | | | |
| **Adverse Events** | | | | | | | | | | |
| **SAEs** | 0.98 (0.71, 1.33) | N/A | | | | N/A | 0.61 (0.13, 2.85) | N/A | N/A | N/A |
| **WDAEs** | 0.57 (0.34, 0.96) | RIS(H) vs. CLZ | 0.74 (0.39, 1.41) | | | 0.54 (0.31, 0.92) | 0.56 (0.34, 0.93) | 0.35 (0.13, 0.97) | 0.55 (0.32, 0.93) | 0.69 (0.37, 1.31) |
| | | OLZ(H) vs. CLZ | 0.36 (0.15, 0.85) | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Adolescent study added | Non-ITT removed | Crossover removed | CLZ < 350 mg/d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **All-Cause WD** | 0.98 (0.81, 1.18) | RIS(H) vs. CLZ | 0.96 (0.70, 1.30) | | | 0.97 (0.80, 1.18) | 0.99 (0.82, 1.19) | 0.90 (0.65, 1.23) | 0.98 (0.81, 1.18) | 0.86 (0.65, 1.14) |
| | | OLZ(H) vs. CLZ | 0.96 (0.69, 1.32) | | | | | | | |
| **Suicidal ideation** | 1.00 (0.06, 15.48) | N/A | | | | | | | | |
| **Suicidal (completed)** | Not estimable | N/A | | | | | | | | |
| **Mortality — all-cause** | 1.02 (0.06, 16.18) | N/A | | | | | | | | |
| **Adverse Events — EPS-Related** | | | | | | | | | | |
| **Akathisia** | 0.88 (0.38, 2.06 | N/A | | | | | | | | |
| **EPS (no. of pts, RR)** | 2.17 (1.33, 3.54) | RIS(H) vs. CLZ | 2.14 (1.29, 3.56) | | | N/A | N/A | N/A | N/A | N/A |
| | | OLZ(H) vs. CLZ | 2.56 (0.39, 16.67) | | | | | | | |
| **EPS Score (ESRS)** | 0.10 (-1.30, 1.51) | N/A | | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Adolescent study added | Non-ITT removed | Crossover removed | CLZ < 350 mg/d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **Parkinsonism** | 0.65 (0.44, 0.97) | RIS(H) vs. CLZ | 0.63 (0.41, 0.97) | | | N/A | N/A | N/A | N/A | N/A |
| | | OLZ(H) vs. CLZ | 0.76 (0.30, 1.95) | | | | | | | |
| **Tardive dyskinesia** | 1.14 (0.45, 2.89) | N/A | | | | | | | | |
| **AIMS** | 0.90 (-0.45, 2.89) | N/A | | | | | | | | |
| **SAS** | -0.80 (-2.03, 0.43) | N/A | | | | | | | | |
| **Adverse Events — Body weight** | | | | | | | | | | |
| **Body weight (kg)** | 0.42 (-1.35, 2.18) | RIS(H) vs. CLZ(R) | -1.71 (-3.05, -0.36) | | | 0.92 (-1.42, 3.25) | N/A | Not pooled* | 0.33 (-1.56, 2.21) | Not pooled* |
| | | OLZ(H) vs. CLZ(R) | 1.78 (-0.66, 4.22) | | | | | | | |
| **Weight gain (no. of pts)** | 0.70 (0.41, 1.19) | RIS(H) vs. CLZ | 0.63 (0.32, 1.22) | | | 0.85 (0.36, 2.03) | N/A | 0.71 (0.40, 1.26) | N/A | N/A |
| | | OLZ(H) vs. CLZ | 0.85 (0.36, 2.03) | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Adolescent study added | Non-ITT removed | Crossover removed | CLZ < 350 mg/d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **Adverse Effects — Metabolic and Other Laboratory Parameters** | | | | | | | | | | |
| **Total Cholesterol (mmol/L)** | -0.16 (-0.47, 0.16) | RIS(H) vs. CLZ(R) | -0.18 (-0.85, 0.49) | | | -0.10 (-0.42, 0.22) | -0.00 (-0.38, 0.38) | N/A | -0.10 (-0.42, 0.22) | -0.14 (-0.57, 0.29) |
| | | OLZ(H) vs. CLZ(R) | -0.15 (-0.52, 0.22) | | | | | | | |
| **Triglycerides (mmol/L)** | -0.82 (-1.65, 0.01) | N/A | | | | N/A | -0.38 (-1.02, 0.26) | N/A | N/A | N/A |
| **FPG (mmol/L)** | 0.10 (-0.31, 0.51) | RIS(H) vs. CLZ(R) | -0.09 (-0.66, 0.48) | | | 0.17 (-0.27, 0.62) | 0.09 (-0.31, 0.49) | N/A | 0.17 (-0.27, 0.62) | 0.07 (-0.42, 0.57) |
| | | OLZ(H) vs. CLZ(R) | 0.30 (-0.29, 0.90) | | | | | | | |
| **A1C** | 0.03 (-0.32, 0.38) | N/A | | | | | | | | |
| **Hyperglycemia** | 0.68 (0.25, 1.82) | RIS(H) vs. CLZ | 0.64 (0.15, 2.72) | | | N/A | 0.77 (0.30, 1.97) | N/A | N/A | N/A |
| | | OLZ(H) vs. CLZ | 0.72 (0.19, 2.77) | | | | | | | |
| **Prolactin (ng/mL)** | 0.29 (0.05, 1.82) | N/A | | | | | | | | |

| Outcome | Reference analysis | Subgroup analysis | | | | Sensitivity analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | < 3 mo removed | Adolescent study added | Non-ITT removed | Crossover removed | CLZ < 350 mg/d removed |
| | | Drugs/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | | | | | |
| **Agranulocytosis** | 0.29 (0.05, 1.82) | RIS(H) vs. CLZ | 0.17 (0.01, 4.11) | | | 0.29 (0.05, 1.82) | N/A | N/A | N/A | 0.17 (0.02, 1.63) |
| | | OLZ(H) vs. CLZ | 0.38 (0.04, 3.56) | | | | | | | |

* Data not pooled due to $I^2$>75%

**Table A4. High-Dose Non-CLZ AAP versus Standard-Dose Non-CLZ APD**

| Outcome | Reference analysis | Subgroup analysis | | | | | | Sensitivity analysis |
|---|---|---|---|---|---|---|---|---|
| | | By add-on drug | | By the number of prior failed APDs | | By comparator drug | | < 3 mo removed |
| | | Drug/strategy | WMD or RR (95% CI) | No. failed APDs | WMD or RR (95% CI) | Comparator | WMD or RR (95% CI) | |
| **Efficacy Outcomes** | | | | | | | | |
| **PANSS-T** | Not pooled* | RIS(H) vs. HAL | -8.70 (-10.91, -6.49) | **1 or more** | -1.30 (-7.91, 5.31) | QUET(H) vs. AAP (QUET) | -1.30 (-7.91, 5.31) | N/A |
| | | QUET(H) vs. QUET(R) | -1.30 (-7.91, 5.31) | **2 or more** | N/A | Non-CLZ AAP(H) vs. TAP(HAL) | -8.70 (-10.91, -6.49) | |
| | | | | **3 or more** | N/A | | | |
| | | | | **# of APD-NR** | -8.70 (-10.91, -6.49) | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **PANSS-P** | Not pooled* | RIS(H) vs. HAL | -2.30 (-3.26, -1.34) | **1 or more** | 0.10 (-1.76, 1.96) | N/A | N/A |
| | | QUET(H) vs. QUET(R) | 0.10 (-1.76, 1.96) | **2 or more** | N/A | | |
| | | | | **3 or more** | N/A | | |
| | | | | **# of APD-NR** | -2.30 (-3.26, -1.34) | | |
| **PANSS-N** | -0.13 (-1.12, 0.86) | RIS(H) vs. HAL | 0.10 (-1.01, 1.21)) | **1 or more** | -1.00 (-3.16, 1.16) | N/A | N/A |
| | | QUET(H) vs. QUET(R) | -1.00 (-3.16, 1.16) | **2 or more** | N/A | | |
| | | | | **3 or more** | N/A | | |
| | | | | **# of APD-NR** | 0.10 (-1.01, 1.21) | | |
| **CGI-S** | -0.10 (-0.61, 0.41) | N/A | | **1 or more** | N/A | N/A | N/A |
| | | | | **2 or more** | N/A | | |
| | | | | **3 or more** | N/A | | |
| | | | | **# of APD-NR** | N/A | | |
| **Response Rate** | 1.27 (0.65, 2.47) | RIS(H) vs. HAL | 2.18 (0.74, 6.41) | **1 or more** | 1.04 (0.74, 1.46) | N/A | N/A |
| | | QUET(H) vs. QUET(R) | 1.04 (0.74, 1.46) | **2 or more** | N/A | | |
| | | | | **3 or more** | N/A | | |
| | | | | **# of APD-NR** | 2.18 (0.74, 6.41) | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Persistence with therapy** | 1.07 (0.82, 1.40) | RIS(H) vs. HAL | 1.25 (0.97, 1.62) | **1 or more** | N/A | AAP | 0.95 (0.79, 1.14) | 1.25 (0.97, 1.62) |
| | | QUET(H) vs. QUET(R) | 0.95 (0.79, 1.14) | **2 or more** | N/A | TAP | 1.25 (0.97, 1.62) | |
| | | | | **3 or more** | N/A | | | |
| | | | | **# of APD-NR** | N/A | | | |
| **Adverse Events** | | | | | | | | |
| **SAE** | 1.47 (0.16, 13.68) | N/A | | | | | | |
| **WDAEs** | 1.09 (0.27, 4.42) | RIS(H) vs. HAL | 0.33 (0.01, 7.74) | | N/A | AAP | 1.47 (0.31, 6.96) | 0.33 (0.01, 7.74) |
| | | QUET(H) vs. QUET(R) | 1.47 (0.31, 6.96) | | N/A | TAP | 0.33 (0.01, 7.74) | |
| | | | | | N/A | | | |
| | | | | | N/A | | | |
| **All-Cause WD** | 0.64 (0.11, 3.60) | RIS(H) vs. HAL | 0.20 (0.03, 1.57) | | N/A | AAP | 1.22 (0.59, 2.55) | 0.20 (0.03, 1.57) |
| | | QUET(H) vs. QUET(R) | 1.22 (0.59, 2.55) | | N/A | TAP | 0.20 (0.03, 1.57) | |
| | | | | | N/A | | | |
| | | | | | N/A | | | |
| **Suicidal ideation** | 1.49 (0.06, 37.37) | N/A | | | | | | |
| **Suicidal (attempted)** | Not estimable | N/A | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Suicidal (attempted)** | Not estimable | N/A | | | | | | |
| **Mortality (all cause)** | Not estimable | N/A | | | | | | |
| **Adverse Events — EPS-Related** | | | | | | | | |
| **EPS (# of patients, RR)** | 0.70 (0.27, 1.79) | RIS(H) vs. HAL | 2.00 (0.20, 20.41) | **1 or more** | N/A | AAP | 0.57 (0.20, 1.59) | N/A |
| | | QUET(H) vs. QUET(R) | 0.57 (0.20, 1.59)) | **2 or more** | N/A | TAP | 2.00 (0.20, 20.41) | |
| | | | | **3 or more** | N/A | | | |
| | | | | **# of APD-NR** | N/A | | | |
| **Tardive dyskinesia** | 0.16 (0.02, 1.52) | N/A | | | | | | |
| **Adverse Events — Body Weight** | | | | | | | | |
| **Body Weight (kg)** | 1.28 (0.04, 2.52) | RIS(H) vs. HAL | 0.60 (-6.75, 7.95) | **1 or more** | N/A | AAP | 1.30 (0.05, 2.55) | N/A |
| | | QUET(H) vs. QUET(R) | 1.30 (0.05, 2.55) | **2 or more** | N/A | TAP | 0.60 (-6.75, 7.95) | |
| | | | | **3 or more** | N/A | | | |
| | | | | **# of APD-NR** | N/A | | | |
| **Weight gain (# of pts)** | 4.40 (0.58, 33.60) | N/A | | | | | | |
| **Adverse Effects — Metabolic and Other Laboratory Parameters** | | | | | | | | |
| **Total** | | | | **1 or more** | N/A | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Cholesterol (mmol/L)** | 0.08 (-0.19, 0.35) | N/A | | **2 or more** | N/A | N/A | N/A |
| | | | | **3 or more** | N/A | | |
| | | | | **# of APD-NR** | N/A | | |
| **Cholesterol — HDL (mmol/L)** | 0.02 (-0.05, 0.09) | N/A | | | | | |
| **Cholesterol — LDL (mmol/L)** | -0.05 (-0.33, 0.23) | N/A | | | | | |
| **Triglycerides (mmol/L)** | 0.31 (-0.22, 0.84) | N/A | | | | | |
| **FPG (mmol/L)** | -0.06 (-0.47, 0.35) | N/A | | | | | |
| **Prolactin (ng/mL)** | -0.43 (-3.56, 2.71) | RIS(H) vs. HAL | -0.87 (-11.07, 9.33) | **1 or more** | N/A | N/A | -0.87 (-11.07, 9.33) |
| | | QUET(H) vs. QUET(R) | -0.38 (-3.67, 2.91) | **2 or more** | N/A | | |
| | | | | **3 or more** | N/A | | |
| | | | | **# of APD-NR** | N/A | | |

* Data not pooled due to $I^2$>75%

# APPENDIX 6: LIST OF INCLUDED RCTS

| Author (Year) | Author (Year) |
|---|---|
| AKDEDE et al. (2005)[42] | KERN et al. (1998)[64] |
| ANIL YAGCIOGLU et al. (2005)[45] | KERN et al. (1999)[62] |
| ASSION et al. (2008)[49] | KOTLER et al. (2004)[47] |
| AZORIN et al. (2001)[60] | KUMRA et al. (2008)[40] |
| BONDOLFI et al. (1998)[66] | KUWILSKY et al. (2010)[55] |
| CHANG et al. (2008)[38] | LINDENMAYER et al. (2003)[57] |
| CITROME et al. (2001)[59] | McEVOY et al. (2006)[70] |
| CLAUS et al. (1992)[68] | MELTZER et al. (2008)[39] |
| CONLEY et al. (1988)[65] | MILLAR et al. (2008)[74] |
| CONLEY et al. (2003)[76] | MOSSAHEB et al. (2006)[73] |
| CZOBOR et al. (2002)[71] | RICHARDSON et al. (2009)[75] |
| FLEISCHHACKER et al. (2010)[54] | ROSENHECK et al. (1999)[63] |
| FREUDENREICH et al. (2007)[41] | SHAFTI (2009)[52] |
| GENC et al. (2007)[50] | SHILOH et al. (1997)[51] |
| GREEN et al. (1997)[67] | TOLLEFSON et al. (2001)[53] |
| HONER et al. (2006)[44] | VOLAVKA et al. (2002)[58] |
| HONER et al. (2011)[72] | VOLAVKA et al. (2004)[56] |
| JOSIASSEN et al. (2005)[46] | WEINER et al. (2010)[69] |
| KANE et al. (2009)[36] | WIRSHING et al. (1999)[61] |
| KELLY et al. (2003)[48] | ZINK et al. (2009)[37] |
| KELLY et al. (2006)[43] | |

# APPENDIX 7: LIST OF EXCLUDED STUDIES

| Author (Year) | Exclusion Reasons |
|---|---|
| ABDOLAHIAN et al. (2008)[145] | Population not of interest |
| ADDINGTON et al. (2004)[146] | Population not of interest |
| ADDINGTON et al. (2009)[147] | Population not of interest |
| ALTAMURA et al. (2002)[148] | Comparators not of interest |
| AMES et al. (1996)[149] | Comparators not of interest |
| AMES et al. (1997)[150] | Comparators not of interest |
| ANON (2007)[151] | Study design not of interest |
| ARANGO et al. (2009)[152] | Population not of interest |
| ARVANITIS et al. (1993)[153] | Article unavailable |
| ATMACA et al. (2003)[154] | Population not of interest |
| AZORIN et al. (2006)[155] | Population not of interest |
| BLIN et al. (1996)[156] | Population not of interest |
| BONDOLFI et al. (2004)[157] | Article unavailable |
| BOUCHARD et al. (1998)[158] | Population not of interest |
| BREIER et al. (1999)[159] | Comparators not of interest |
| BREIER et al. (2000)[160] | Article unavailable |
| BREIER et al. (2001)[161] | Comparators not of interest |
| BREIER et al. (2001)[162] | Comparators not of interest |
| BROOK (2000)[163] | Study design not of interest |
| CANUSO et al. (2009)[164] | Comparators not of interest |
| CANUSO et al. (2009)[165] | Comparators not of interest |
| CAROTHERS et al. (2009)[166] | Comparators not of interest |
| CESKOVA et al. (1994)[167] | Population not of interest |
| CETIN et al. (1999)[168] | Population not of interest |
| CHAPEL et al. (2009)[169] | Population not of interest |
| CHEN et al. (1998)[170] | Non-English/French |
| CHEN et al. (2005)[171] | Non-English/French |
| CHOUINARD (1995)[172] | Comparators not of interest |
| CHOUINARD et al. (1993)[173] | Population not of interest |
| CILIBERTO et al. (2005)[174] | Population not of interest |
| CITROME et al. (2009)[175] | Population not of interest |
| CITROME et al.(2003)[176] | Duplicate |
| CONLEY et al. (1999)[177] | Study design not of interest |
| CORRELL (2005)[178] | Study design not of interest |
| CROCKET et al. (1992)[179] | Population not of interest |
| CSERNANSKY et al. (2002)[180] | Population not of interest |
| DAVIDSON et al. (2007)[181] | Population not of interest |
| EDGELL et al. (2000)[182] | Population not of interest |
| EKBLOM et al. (1974)[183] | Population not of interest |
| EMSLEY (1999)[184] | Population not of interest |
| FANOUS et al. (1999)[185] | Study design not of interest |
| FINDLING et al. (2010)[186] | Population not of interest |
| FLEISCHHACKER et al. (1995)[187] | Article unavailable |
| FLEISCHHACKER et al. (2003)[188] | Study design not of interest |

| Author (Year) | Exclusion Reasons |
|---|---|
| FLYNN et al. (1998)[189] | Study design not of interest |
| FREUDENREICH (2009)[190] | Article unavailable |
| GARCIA et al. (2009)[191] | Comparators not of interest |
| GUO et al. (2003)[192] | Non-English/French |
| GUREJE et al. (2003)[193] | Population not of interest |
| HALE et al. (1996)[194] | Comparators not of interest |
| HANSSENS et al. (2008)[195] | Comparators not of interest |
| HARRIGAN et al. (2004)[196] | Population not of interest |
| HARVEY et al. (2004)[197] | Population not of interest |
| HARVEY et al. (2006)[198] | Population not of interest |
| HARVEY et al. (2008)[199] | Comparators not of interest |
| HATTA et al. (2009)[200] | Population not of interest |
| HECK et al. (2000)[201] | Population not of interest |
| HENDERSON et al. (2009)[202] | Population not of interest |
| HENDERSON et al. (2009)[203] | Study design not of interest |
| HIRSCH et al. (1994)[204] | Comparators not of interest |
| HIRSCH et al. (1996)[205] | Study design not of interest |
| HONG et al. (1997)[206] | Comparators not of interest |
| HOUGH et al. (2011)[207] | Population not of interest |
| HOYBERG et al. (1993)[208] | Population not of interest |
| HUTTUNEN et al. (1995)[209] | Population not of interest |
| HWANG et al. (2003)[210] | Population not of interest |
| ISHIGOOKA et al. (2001)[211] | Population not of interest |
| JAYATHILAKE et al. (2005)[212] | Duplicate |
| JIA et al. (2000)[213] | Non-English/French |
| JOSIASSEN et al. (2003)[214] | Duplicate |
| KANE et al. (1988)[77] | Comparators not of interest |
| KANE et al. (1996)[215] | Comparators not of interest |
| KANE et al. (2001)[88] | Comparators not of interest |
| KANE et al. (2003)[216] | Population not of interest |
| KANE et al. (2006)[217] | Comparators not of interest |
| KANE et al. (2010)[218] | Comparators not of interest |
| KANE et al. (2010)[219] | Population not of interest |
| KIM et al. (2009)[220] | Population not of interest |
| KINON et al. (2000)[221] | Article unavailable |
| KINON et al. (2001)[222] | Article unavailable |
| KINON et al. (2008)[223] | Population not of interest |
| KINON et al. (2010)[224] | Population not of interest |
| KRAKOWSKI et al. (2006)[225] | Population not of interest |
| KRAKOWSKI et al. (2009)[226] | Population not of interest |
| KREININ et al. (2006)[227] | Population not of interest |
| LASSER et al. (2004)[228] | Study design not of interest |
| LI et al. (1999)[229] | Non-English/French |
| LI et al. (2003)[230] | Non-English/French |
| LIEBERMAN et al. (2005)[231] | Comparators not of interest |
| LIEBERMAN et al. (2005)[232] | Comparators not of interest |
| LIEBERMAN et al. (2006)[233] | Article unavailable |

| Author (Year) | Exclusion Reasons |
|---|---|
| LIN et al. (2010)[234] | Population not of interest |
| LINDENMAYER et al. (1997)[235] | Study design not of interest |
| LINDENMAYER et al. (1998)[236] | Study design not of interest |
| LINDSTROM et al. (1994)[237] | Population not of interest |
| LINK et al. (1995)[238] | Comparators not of interest |
| LIU et al. (1996)[239] | Non-English/French |
| LIU et al. (2001)[240] | Non-English/French |
| LIU et al. (2005)[241] | Non-English/French |
| LIU et al. (2005)[242] | Non-English/French |
| LIU et al. (2005)[243] | Non-English/French |
| LOEBEL et al. (2006)[244] | Comparators not of interest |
| LOEBEL et al. (2006)[245] | Comparators not of interest |
| MARDER et al. (1994)[246] | Population not of interest |
| MARDER et al. (2005)[247] | Comparators not of interest |
| MARDER et al. (2006)[248] | Comparators not of interest |
| MAURI et al. (2006)[249] | Comparators not of interest |
| MCCUE et al. (2006)[250] | Population not of interest |
| McEVOY (1994)[251] | Study design not of interest |
| MELTZER et al. (2003)[252] | Population not of interest |
| MELTZER et al. (2007)[253] | Comparators not of interest |
| MICELI et al. (2003)[254] | Population not of interest |
| MICELI et al. (2010)[255] | Population not of interest |
| MICELI et al. (2010)[256] | Population not of interest |
| MIN et al. (1993)[257] | Comparators not of interest |
| MITCHELL et al. (2006)[258] | Population not of interest |
| MOLLER et al. (1997)[259] | Population not of interest |
| MURASAKI et al. (1995)[260] | Article unavailable |
| NASRALLAH et al. (2004)[261] | Population not of interest |
| NASRALLAH et al. (2008)[262] | Comparators not of interest |
| NASRALLAH et al. (2010)[263] | Comparators not of interest |
| NOSE et al. (2009)[264] | Study design not of interest |
| O'CONNOR et al. (1999)[265] | Article unavailable |
| OKUGAWA et al. (2009)[266] | Population not of interest |
| ONO et al. (2008)[267] | Comparators not of interest |
| ORTEGA-SOTO et al. (1997)[268] | Article unavailable |
| OU (2007)[269] | Non-English/French |
| PANDINA et al. (2009)[270] | Comparators not of interest |
| PENG et al. (2001)[271] | Non-English/French |
| PENN et al. (2009)[272] | Comparators not of interest |
| PEREZ et al. (2003)[273] | Population not of interest |
| PEUSKENS (1995)[274] | Population not of interest |
| POTKIN et al. (2002)[275] | Population not of interest |
| POTKIN et al. (2006)[276] | Comparators not of interest |
| POTKIN (1997)[277] | Population not of interest |
| RAPPARD et al. (2006)[278] | Comparators not of interest |
| REEVES et al. (1996)[279] | Comparators not of interest |
| RIEDEL et al. (2007)[280] | Comparators not of interest |

| Author (Year) | Exclusion Reasons |
|---|---|
| ROSENHECK et al. (1999)[281] | Comparators not of interest |
| RUPNOW et al. (2005)[282] | Comparators not of interest |
| RUPNOW et al. (2007)[283] | Study design not of interest |
| SALGANIK et al. (1998)[284] | Comparators not of interest |
| SANGER et al. (1997)[285] | Population not of interest |
| SHAW et al. (2006)[286] | Comparators not of interest |
| SHOPSIN et al. (1979)[287] | Population not of interest |
| SHUN et al. (2000)[288] | Non-English/French |
| SIMPSON et al. (1997)[289] | Population not of interest |
| SIMPSON et al. (2005)[290] | Comparators not of interest |
| SIROTA et al. (2006)[291] | Comparators not of interest |
| SMITH et al. (2001)[292] | Study design not of interest |
| STROUP et al. (2007)[293] | Comparators not of interest |
| STROUP et al. (2009)[294] | Study design not of interest |
| STROUP et al. (2006)[295] | Population not of interest |
| SUN (2000)[296] | Non-English/French |
| SUPPES et al. (1999)[297] | Population not of interest |
| TAKAHASHI et al. (1999)[298] | Comparators not of interest |
| TAO et al. (2006)[299] | Non-English/French |
| TAYLOR et al. (2008)[300] | Comparators not of interest |
| TOLLEFSON et al. (1997)[301] | Population not of interest |
| TOWNSEND et al. (2004)[302] | Comparators not of interest |
| TRAN et al. (1997)[303] | Population not of interest |
| TZIMOS et al. (2006)[304] | Comparators not of interest |
| TZIMOS et al. (2007)[305] | Comparators not of interest |
| VERSAVEL et al. (2005)[306] | Comparators not of interest |
| WANG et al. (2005)[307] | Non-English/French |
| WANG et al. (2010)[308] | Population not of interest |
| WIRSHING et al. (1996)[309] | Comparators not of interest |
| WRIGHT et al. (2001)[310] | Comparators not of interest |
| WU (2002)[311] | Non-English/French |
| WU et al. (2005)[312] | Non-English/French |
| XIE et al. (2001)[313] | Non-English/French |
| YANG et al. (1994)[314] | Non-English/French |
| YAO, (1999)[315] | Non-English/French |
| YEN et al. (2004)[316] | Population not of interest |
| YING et al.[317] | Non-English/French |
| ZHANG et al. (2000)[318] | Non-English/French |
| ZHANG et al. (2002)[319] | Non-English/French |
| ZHANG et al. (2003)[320] | Non-English/French |
| ZHANG et al. (2003)[321] | Non-English/French |
| ZHANG et al. (2004)[322] | Non-English/French |
| ZHONG et al. (2006)[323] | Comparators not of interest |
| ZHU et al. (1999)[324] | Non-English/French |
| ZHU et al. (2001)[325] | Non-English/French |
| ZHU et al. (2002)[326] | Non-English/French |

# APPENDIX 8: LIST OF RCTS REPORTED IN MULTIPLE PUBLICATIONS

| Author (Year) | Publication Status | Main Outcomes Reported |
|---|---|---|
| **(RIS+CLZ) versus (Placebo+CLZ)** | | |
| AKDEDE et al. (2005)[42] | Full text | Cognition |
| ANIL YAGCIOGLU et al. (2005)[45] | Full text | Efficacy and safety |
| **RIS (H) or OLZ(H) versus CLZ ( R ) or Halo** | | |
| CITROME et al. (2001)[59] | Full text | Effects on hostility |
| CZOBOR et al. (2002)[71] | Full text | Antipsychotic-induced weight gain |
| LINDENMAYER et al. (2003)[57] | Full text | Glucose and cholesterol |
| VOLAVKA et al. (2004)[56] | Full text | Effects on prolactin |
| VOLAVKA et al. (2002)[58] | Full text | PANSS, WDAE, safety, etc. |
| **OLZ(H) versus CLZ ( R )** | | |
| CONLEY et al. (2003)[76] | Letter to editor | Main results (BPRS, CGI-S, etc.) were reported in this letter |
| KELLY et al. (2006)[43] | Full text | Relationship of high-dose OLZ plasma concentration to symptoms, AE, etc. |
| KELLY et al. (2003)[48] | Full text | AE and metabolic outcomes |
| **RIS (H) versus Halo** | | |
| GREEN et al. (1997)[67] | Full text | Effect on verbal working memory |
| KERN et al. (1999)[62] | Full text | Effect on secondary memory |
| KERN et al. (1998)[64] | Full text | Effect on reaction time, manual dexterity, and motor learning |
| WIRSHING et al. (1999)[61] | Full text | PANSS and CGI etc. |
| **(RIS+CLZ) versus (ZIP+CLZ)** | | |
| KUWILSKY (2010)[55] | Full text | Outcomes (PANSS, safety, etc.) assessed at 26 weeks and 52 weeks |
| ZINK et al (2009)[37] | Full text | Outcomes (PANSS, safety, etc.) initially assessed at 6 weeks |

# APPENDIX 9: INCLUSION AND EXCLUSION CRITERIA REPORTED IN INCLUDED RCTS

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| AKDEDE et al. (2005)[42] | Aged 18–55 years with schizophrenia and schizoaffective diagnosed with DSM-IV criteria; on treatment of CLZ at least 6 months (300–900 mg/d); having residual schizophrenia (negative symptom was more prominent than positive symptom; history of failure to respond to at least two APDs other than CLZ. CLZ dose has not been changed for at least for 1 month prior to screening. Only patients whose level of positive symptom was stable by clinical criteria and reported in written notes for at least 3 months prior to study entry were included. | Patients who were concomitantly receiving mood stabilizer, antidepressants, APDs other than CLZ; history of intolerance to risperidone for reasons other than EPS, or who had EPS that were not responsive to the addition of anticholinergic medication when receiving risperidone ≤ 6 mg/d; history of alcohol or substance dependence within 3 months of protocol entry. |
| ANIL YAGCIOGLU et al. (2005)[45] | Aged 18–55 years with schizophrenia and schizoaffective diagnosed with DSM-IV criteria; on treatment of CLZ at least 6 months (300–900 mg/d); having residual schizophrenia (negative symptom was more prominent than positive symptom; history of failure to respond to at least two APDs other than CLZ. CLZ dose has not been changed for at least for 1 month prior to screening. Only patients whose level of positive symptom was stable by clinical criteria and reported in written notes for at least 3 months prior to study entry were included. | Patients who were concomitantly receiving mood stabilizer, antidepressants, APDs other than CLZ; history of intolerance to risperidone for reasons other than EPS, or who had EPS that were not responsive to the addition of anticholinergic medication when receiving risperidone ≤ 6 mg/d; history of alcohol or substance dependence within 3 months of protocol entry. |
| ASSION et al. (2008)[49] | Male and female patients, age 18–70 years, chronic schizophrenia, at least moderately ill (CGI score ≥ 4); already on a stable dose of CLZ for at least 3 months; partial or no response to CLZ, no intake of other APDs except CLZ in the last 3 months prior to trial; ClZ serum level had to be within therapeutic range. | Suicidal tendencies at the time of screening; female patients of child-bearing potential with a positive pregnancy test or were breastfeeding; participating in another trial or taking investigational drugs within 3 months before entering the study; alcohol or substance misuse or dependency; medical disorders being the major causative factor for psychotic symptoms, hyperprolactinemia or known non-response to amisulpride. |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| AZORIN et al. (2001)[60] | Male and female patients aged 18–65 years who met DSM-IV criteria for schizophrenia (disorganized, catatonic, paranoid, residual, or undifferentiated) were eligible for recruitment. Only those with baseline scores of at least 4 on the Clinical Global Impression (CGI) scale, at least 45 (total score) on the Brief Psychiatric Rating Scale (BPRS), and at least 4 on two or more of the four core symptoms (unusual thought content, hallucinations, conceptual disorganization, suspiciousness) were randomly assigned to treatment with either clozapine or risperidone. Both in-patients and outpatients were recruited to the study. Patients were additionally required to meet the following minimum criteria for poor response to previous treatment: 1) The patient's current episode had been treated continually with a neuroleptic for at least the preceding 6 months without significant clinical improvement. 2) The patient had undergone one unsuccessful trial of antipsychotic medication equivalent to 20 mg/day of haloperidol for at least 6 weeks (less if the patient was experiencing dose-limiting adverse events) since the onset of the current episode. If several drugs had been prescribed simultaneously, the final equivalence dosage could be calculated by adding the individual equivalencies. 3) The patient had experienced no period of good functioning for at least 24 months despite a sufficient period of use of two antipsychotics from at least two chemical classes, or no period of good functioning for 5 years despite the use of three antipsychotics. Poor previous treatment response as defined in the current study differs from treatment resistance by having a less stringent criterion for the previous drug history than did the study by Kane et al.,[77] enabling patients to be more representative of those seen in current clinical practice compared with previous clinical trials. | Patients were excluded if they had a history of medical conditions or drug treatment that might put them at special risk or bias the assessment of their clinical or mental status (e.g., epilepsy requiring continuous treatment, active blood dyscrasias, leukopenia, chronic obstructive lung disease or pulmonary emphysema, cardiovascular disease or recent myocardial infarction, significantly impaired renal or hepatic function, active problems with urinary retention or narrow angle glaucoma, toxic psychosis, chemical dependence, or moderate to severe mental retardation). Those previously treated with clozapine or risperidone were excluded from the trial. Patients likely to require continuous treatment with other psychotropic agents, anticholinergics, or drugs likely to lower white blood cell count were also excluded, as were women of childbearing potential who were not practicing a medically approved form of birth control. |
| BONDOLFI et al. (1998)[66] | Aged 18–65 years (one patient was 17.4 years old) and met the DSMIII-R criteria for chronic schizophrenia. They had previously failed to respond to or were intolerant of at least two different classes of antipsychotic drugs given in appropriate doses for at least 4 weeks each. No subject had previously received clozapine. A total score of 60– | Women of reproductive age who were not using adequate contraception; pregnant or lactating women; patients with epilepsy, other substantial organic or neurologic disease, or clinically relevant abnormal electrocardiograms or laboratory tests; patients with a history of alcohol or drug abuse within the previous 12 months; and patients who |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| | 120 on the Positive and Negative Syndrome Scale was required. | had been in trials of investigational new drugs during the preceding 4 weeks. |
| CHANG et al. (2008)[38] | Schizophrenia patients diagnosed with DSM-IV criteria; aged 18–65 years; documented treatment failure prior to CLZ treatment; CLZ treatment for more than 1 year with at least 8 weeks at a stable daily dose of 400 mg or more, unless companied by adverse effects; no change in CLZ daily dose or other concomitant medication for more than 3 months, indicating a plateau of clinical response to CLZ; either BPRS total score of at least 35 or more than 2 in SANS global rating items scores of at least 3. The minimum positive symptom total score of at least 8 on 4 items of the BPRS or a score of at least 4 on any one of the following items: hallucinatory behaviour, conceptual disorganization, unusual thought content, or suspiciousness. Fluency in written and spoken Korean. | DSM-IV–defined substance dependence (excluding nicotine and caffeine) mental retardation, pregnancy or lactation; neurologic disorders including epilepsy, stroke, or severe head trauma; prior history of no response to aripiprazole; participating in a clinical trial of another investigational drug within 3 months prior to the study; treatment with an injectable depot neuroleptic within less than 3 month intervals between the last depot neuroleptic injection and baseline; history of electroconvulsive therapy within the previous 3 months; or difficulty in understanding written and spoken Korean. |
| CITROME et al. (2001)[59] | See VOLAVKA et al. (2002)[58] | See VOLAVKA et al. (2002)[58] |
| CLAUS et al. (1992)[68] | Aged ≥ 18 years, schizophrenia diagnosed by DSM-III-R; had to be hospitalized; despite optimization of conventional neuroleptic treatment, they still presented positive, negative and/or EPS; duration of hospitalization due to mental disorder was to be less than 10 years. | Patients with clinical relevant organic disorders, pregnant or lactating patients, or women in their reproductive phase without adequate contraceptive measures. |
| CONLEY et al. (1988)[65] | Physically healthy schizophrenia patients diagnosed by DSM-III-R; inadequately controlled on at least two antipsychotics and plus failed to respond to haloperidol trial defined as less than a 20% decrease in total BPRS score; an endpoint BPRS score greater than 35, and a CGI severity score greater than 4 for patients completing at least 2 weeks of haloperidol therapy. (See Appendix for definition of inadequately controlled.) Subjects in the present study could have had prior clozapine treatment but could not have demonstrated resistance to clozapine. | NR |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| CONLEY et al. (2003)[76] | Diagnosed with DSM-IV schizophrenia, medically healthy and treatment resistant (see Appendix on inadequate response criteria). | Patients previously failing clozapine treatment. |
| CZOBOR et al. (2002)[71] | See VOLAVKA et al. (2002)[58] | See VOLAVKA et al. (2002)[58] |
| FLEISCHHACKER et al. (2010)[54] | Patients aged 18–65 years with DSM-IV-TR criteria for schizophrenia, stable dose of CLZ for ≥ 3 months. Patients not optimally controlled on CLZ and had to have experienced ≥ 2.5 kg weight gain during CLZ treatment. | Patients at risk for suicide (active, clinically significant suicidal ideation, or recently attempted suicide), diagnosis of schizoaffective disorder, bipolar disorder, depression with psychotic symptoms, or organic mental disorders. Anyone meeting DSM-IV-TR criteria for any significant psychoactive substance use disorder within 3 months was excluded, as were those with history of neuroleptic malignant syndrome, epilepsy, seizures or stroke, history/evidence of other medical conditions that would expose patients to undue risk or interfere with study assessments. Excluded pregnant, breastfeeding women or those unwilling to use a suitable method of contraception. |
| FREUDENREICH et al. (2007)[41] | Subjects had schizophrenia as their primary diagnosis and displayed stable residual psychiatric symptoms as defined by a PANSS score greater than 60. Diagnoses were based on physician interview and chart review (O.F.), using DSM-IV criteria (American Psychiatric Association Committee on Nomenclature and Statistics, 1994). Patients had to have failed at least two previous trials of antipsychotics prior to clozapine (as determined by chart review) and be currently treated with clozapine monotherapy for at least 6 months, at a stable dose for at least 8 weeks and with clozapine plasma levels of at least 200 ng/mL, unless the clozapine dose necessary to achieve that level was not tolerated (VanderZwaag et al. 1996). Ancillary, stable psychotropics were allowed. | Patients were excluded if there was an active substance use disorder by chart review, an unstable medical illness, or suicidal ideation. Patients were also excluded if they had any cognitive disorder (including mental retardation) or developmental disorder. |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| GENC et al. (2007)[50] | (1) Diagnosis of schizophrenia (DSM-IV criteria); (2) aged 18–50 years; (3) partial response to at least a 12-week trial of 400 to 600 mg/d of clozapine (partial response was defined as persistent psychotic symptoms, as evidenced by a total score > 45 on the BPRS [on which each of 18 items is scored from 1 to 7] or a rating of moderately ill [> 4] on at least 2 of the 4 BPRS positive symptom items [hallucinatory behaviour, conceptual disorganization, unusual thought content, and suspiciousness]); and (4) voluntary participation in the study with signed informed consent. | Patients with comorbid substance abuse, organic mental disorders, epilepsy, mental retardation, and severe physical illness were excluded from the study. |
| GREEN at al. (1997)[67] | DSM-III-R criteria for schizophrenia as defined by Structured Clinical Interview; treatment-resistant; symptom severity criteria including 1) total score of at least 45 on 18-item BPRS; 2) minimum score of 4 on 2 of the following BPRS items: conceptual disorganization, suspiciousness, hallucinations, and unusual thought concern; and 3) CGI rating of at least 4. | Clinically significant neurological disease (including seizure disorder) as determined by physical examination, laboratory tests, and medical history; a history of head injury; physical, cognitive or language impairment of such severity as to adversely affect validity of clinical ratings; history of substance abuse as defined by DSM-III-R within past 6 months; previous trial of risperidone that was sufficient to determine clinical response; treatment with investigational drugs or clozapine within the previous 4 weeks or depot neuroleptics within the past 8 weeks; behaviour posing a significant danger to self or others; significant clinical improvement (i.e., BPRS total score of 35 or less) shown between initial screening and start of study. |
| HONER et al. (2006)[44] | The inclusion criteria were a diagnosis of schizophrenia or schizoaffective disorder by DSM-IV; aged 18–65 years; treatment with clozapine for the indication of poor response to other antipsychotic agents; treatment for at least 12 weeks at a stable dose of 400 mg or more per day, unless the size of the dose was limited by side effects; a total score of 80 or greater at baseline on the PANSS; a CGI score of 4 or greater; and a Social and Occupational Functioning Assessment Scale (SOFAS) 18 score of 40 or less. | The exclusion criteria were clinically significant alcohol or substance abuse in the previous 3 months, developmental disability, current treatment with clozapine for the primary indication of movement disorder or of intolerable side effects from other medications, or previous treatment with clozapine augmented with risperidone. |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| HONER et al. (2011)[72] | Diagnosis of schizophrenia or schizoaffective disorder (DSM-IV), aged 18–65 years, total score of 70–110 on PANSS with persistent positive (score ≥ 15 on PANSS positive subscale, with a score ≥ 4 on at least 1 of: delusions, conceptual disorganization, hallucinations, or suspiciousness) and/or negative (score ≥ 15 on PANSS negative subscale, with a score ≥ 4 on at least 1 of: blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, or lack of spontaneity) symptoms, and with a CGI score of at least 4, without a 30% or greater improvement in PANSS score during the 4 week open-label 800 mg quetiapine phase. | Level 6 treatment resistance according to the May scale; significant alcohol or substance abuse in the previous 3 months, significant medical illness, previous treatment with quetiapine > 800 mg/day, or previous treatment with clozapine. Subjects with a 30% or greater improvement in PANSS during the 4 week open label 800 mg quetiapine phase were also excluded. |
| JOSIASSEN et al. (2005)[46] | 1) Had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder; 2) were aged 20–65 years; 3) had, before treatment with clozapine, documented treatment failure after two antipsychotics approved by the US Food and Drug Administration were administered for an adequate duration in a sufficient dose (6 or more weeks of 1,000 mg/day of chlorpromazine equivalents); 4) demonstrated a documented failure to show a satisfactory clinical response to an adequate trial of clozapine (3 or more months of at least 600 mg/day of oral clozapine or a plasma drug level of 350 ng/mL or higher); and 5) had persistent psychotic symptoms, as evidenced by either a total score of at least 45 on the BPRS (on which each of 18 items is scored from 1 to 7) or a rating of moderately ill (4 or more) on at least two of the four BPRS positive symptom items (hallucinatory behaviour, conceptual disorganization, unusual thought content, and suspiciousness). | NR |
| KANE et al. (2009)[36] | 1) Outpatients of either gender; 2) age ≥ 18 years with chronic, stable schizophrenia or schizoaffective disorder and currently receiving a stable dose of quetiapine (400–800 mg/d) or risperidone (4–8 mg/d) for ≥ 4 weeks but with an inadequate response; 3) the patient must not have shown significant improvement or worsening of symptoms within 1 month of screening; 4) Inadequate response was primarily defined by investigators' judgment as a CGI-S score of 4 to 6; 5) patients have shown previous antipsychotic responsiveness (except with clozapine) | 1) A history of clozapine failure; 2) hospitalization due to their psychiatric illness in the past 3 months; 3) first episode of schizophrenia or schizoaffective disorder within the past year; 4) acute depression during the past month; 5) previous participation in a trial within the past month or any aripiprazole clinical trial; 6) suicidal ideation; 7) substance abuse/dependence; or 8) a history of seizure disorder. Patients were also ineligible if they had any medically significant abnormal laboratory test or vital sign or any medical condition that |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| | in the past 12 months. Women of childbearing potential (not pregnant or breastfeeding) were permitted if they had had a negative pregnancy test within 72 hours pre-study and were using contraception. | could interfere with assessments or expose them to unnecessary risk. |
| KELLY et al. (2003)[48] | Diagnosed with DSM-IV schizophrenia; medically healthy; and treatment resistant: 1) Persistent positive psychotic symptoms: item score ≥ 4 (moderate) on at least 2 of 4 positive symptom items on BPRS; 2) the current presence of at least moderately severe illness as rated by the total BPRS score (score ≥ 45 on the 18-item scale) and a score of ≥ 4 (moderate) on the CGI; 3) two failed historical trials of antipsychotics of at least 6 weeks' duration at doses of at least 600 mg/d chlorpromazine equivalents; and 4) no stable period of good social and/or occupational functioning within the last 5 years. | NR, see KELLY et al. (2006)[43] |
| KELLY et al. (2006)[43] | Diagnosed with DSM-IV schizophrenia and treatment resistant (See Kelly et al. 2003[48]) | Patients with a documented history of clozapine failure. |
| KERN et al. (1998)[64] | See GREEN at al. (1997)[67] | See GREEN at al. (1997)[67] |
| KERN et al. (1999)[62] | See GREEN at al. (1997)[67] | See GREEN at al. (1997)[67] |
| KOTLER et al. (2004)[47] | The study population comprised chronic schizophrenia (as defined by DSM-IV criteria) day-patients, aged 18–60 years, all with illnesses of longer than 2 years' duration and with a minimum score of at least 70 on PANSS (Kay et al. 1987). All subjects met parameters for treatment resistance following the criteria of Kane et al. (1988).[77] Participating subjects to have been maintained on a stable dose of their olanzapine monotherapy for at least 6 months before study commencement. | Patients with any significant medical or neurological illness, or who were pregnant, were not included in the study. The absence of medical or neurological illness was verified by means of routine laboratory investigation, physical and neurological examination, treating physician report, and medical records. Patients who were receiving mood-stabilizers or any other psychoactive medication before study commencement were not included in the study. |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| KUMRA et al. (2008)[40] | Boys and girls aged 10–18 years, diagnosed with schizophrenia or schizoaffective disorder, meet study criteria for treatment-refractory. | Excluded if they had received a premorbid diagnosis of mental retardation (i.e., full-scale IQ < 70), had a history of serious adverse reactions to the proposed treatment; were pregnant; in a serious and unstable medical condition; or if they had failed an adequate trial of clozapine (at least 12 weeks) at adequate doses (300 mg/d or higher) and/or had failed an adequate trial of OLZ at least 8 weeks at 20 mg/d or higher. |
| KUWILSKY et al. (2010)[55] | See ZINK et al. (2009)[37] | See ZINK et al. (2009)[37] |
| LINDENMAYER et al. (2003)[57] | See VOLAVKA et al. (2002)[58] | See VOLAVKA et al. (2002)[58] |
| McEVOY et al. (2006)[70] | Patients were aged 18–65 years, diagnosed with schizophrenia (based on DSM-IV); patients with inadequate resolution of psychopathology, or marked sensitivity to EPS were recommended to enter this study and decision-making capacity to provide informed consent. | Exclusion criteria were mental retardation, other cognitive disorders, or past serious adverse reactions to any of the proposed treatments. Patients experiencing first psychotic episodes, patients with past evidence of profound treatment resistance; women who were pregnant or breastfeeding, or patients with serious, unstable medical conditions. |
| MELTZER et al. (2008)[39] | 1) Patients with schizophrenia or schizoaffective disorders; 2) aged 18–58 years; 3) treatment resistant based on Kane's criteria.[77] | History of non-response to adequate trial of conventional dose of CLZ or OLZ; history of substantial neurologic disorder, cardiac disorder, or active substance abuse. |
| MILLAR et al. (2008)[74] | Schizophrenia patients suboptimally controlled on CLZ treatment (at least 3 months) and body weight gained ≥ 2.5 kg since CLZ treatment. | NR |
| MOSSAHEB et al. (2006)[73] | 1) Schizophrenia patients; 2) resistant to 2 adequate trials of 2 different classes of APDs and to a trial with CLZ in an adequate dosage for ≥ 6–8 weeks. | NR |
| RICHARDSON et al. (2009)[75] | DSM-IV schizophrenia or schizoaffective disorders who continued to manifest moderate illness severity (18 items BPRS total ≥ 45 and CGI-S ≥ 4 and persistent psychosis (4 psychosis item total ≥ 8, with 1 of these items ≥ 4) despite adequate prior CLZ treatment | NR |
| ROSENHECK et al. (1999)[63] | Clinical eligibility criteria modelled on those of Kane et al. (1988), diagnosis of schizophrenia (DSM-IIIR), refractory despite 2 treatments with APDs, severe symptoms indicated by scores on the BPRS and CGI scale, and serious social dysfunction for the previous 2 years. | Excluded if they were unable to give informed consent or had a previous trial of CLZ, had a current myeloproliferative disorder, or were pregnant. |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| SHAFTI (2009)[52] | Symptoms of schizophrenia, poor response to OLZ (less than 25% decrement in total SAPS score) with a maximum dose of 25 mg/d for at least 4 weeks. | NR |
| SHILOH et al. (1997)[51] | Patients who exhibited a partial and unsatisfactory response to CLZ following at least 12 weeks of treatment in adequate dose. Met DSM-IV criteria for schizophrenia; failed to respond to at least 3 types of TAP at adequate doses for a period of not less than 6 weeks. | Known history of drug or substance misuse, past record of noncompliance to medical treatments, concomitant treatment with other medications, and any evidence of past bone marrow suppression or seizure disorder. |
| TOLLEFSON et al. (2001)[53] | Patients aged 18–70 years who met DSM-IV criteria for schizophrenia and who had a minimum BPRS of at least 45 and a score of 4 or more on at least 2 items of the PANSS-positive score. | Patients who had previously been treated with OLZ or who were OLZ or CLZ nonresponders; patients intolerant to either OLZ or CLZ. |
| VOLAVKA et al. (2002)[58] | In-patients aged 18–60 years with a diagnosis of DSM-IV chronic schizophrenia or schizoaffective disorder and suboptimal response to previous treatment, which was defined by 2 criteria that needed to be present. The first criterion of suboptimal response was persistent positive symptoms (hallucinations, delusions, or marked thought disorder) after at least 6 contiguous weeks of treatment, presently or documented in the past, with one or more typical antipsychotics at doses ≥ 600 mg/day in chlorpromazine equivalents. The second criterion was a poor level of functioning over the past 2 years, defined by the lack of competitive employment or enrolment in an academic or vocational program and not having age-expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained. | Had a history of nonresponse to clozapine, risperidone, or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for at least 6 weeks, or clozapine for at least 14 weeks. The longer clozapine trial duration was required because Meltzer et al. observed that less than 50% of patients who improve with clozapine reach that improvement within the first 6 weeks of treatment. Patients with a history of clozapine, olanzapine, risperidone, or haloperidol intolerance as well as those who received a depot antipsychotic within 30 days before randomization were also excluded. |
| VOLAVKA et al. (2004)[56] | See VOLAVKA et al. (2002)[58] | See VOLAVKA et al. (2002)[58] |
| WEINER et al. (2010)[69] | In-patients or outpatients aged 18–65 years meeting DSM-IV criteria for schizophrenia or schizoaffective disorder in clinically stable, nonacute phase who were treatment resistant, defined as BPRS total score ≥ 45 or CGI-S ≥ 4, and BPRS positive score ≥ 8, with one or more item rated ≥ 4. Adequate trial of clozapine, where clozapine treatment was ≥ 6 months on a dose producing clozapine plasma level ≥ 350 mg/mL or clozapine+norclozapine level ≥ 450 ng/mL | DSM-IV diagnosis of substance or alcohol abuse (other than nicotine) within the past month; alcohol or substance abuse (other than nicotine) within the past 6 months; mental retardation; unstable medical conditions; previously treated with ≥ 8 mg/day of risperidone for at least 6 weeks. |

| Author | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| WIRSHING et al. (1999)[61] | Subjects were included if they were aged 18–60 years, had a diagnosis of schizophrenia, were able to take oral medication, were able to adhere to the required schedule of evaluations. | Excluded if they had significant medical disease, had a history of seizure disorder, or had taken any investigational drug during the 4 weeks before the start of the study. No physical or cognitive impairment so as they could not give consent. No substance abuse 2 months prior, substance dependence 6 months prior. History of violence or a history of risperidone treatment failure |
| ZINK et al. (2009)[37] | 1) Diagnosis of schizophrenic or schizoaffective psychosis (DSM-IV); 2) aged 18–70 years; 3) able to give informed consent; 4) women capable of contraception; 5) documented treatment failures with at least 2 anti-psychotic agents before being switched to CLZ; 6) treatment-resistant symptoms of psychosis under CLZ monotherapy with clinical significance. | Anyone not covered by inclusion criteria, intolerability to risperidone or ziprasidone and substance abuse except for nicotine. |

# APPENDIX 10: STUDY LEVEL DEFINITION OF "INADEQUATE RESPONSE" TO APD TREATMENT IN INCLUDED RCT

| Author (Year) | Definition of "Inadequate Response" for Inclusion in RCT |
|---|---|
| AKDEDE et al. (2005)[42] | Failed at least two adequate duration and dose of antipsychotics other than CLZ; plus on CLZ (300–900 mg/d) at least 6 months; PANSS ≥ 72; CGI-S ≥ 4; a score of at least 3 on any 1 of PANSS-Positive subscale items (0–7 scale) were required for entry. |
| ANIL YAGCIOGLU et al. (2005)[45] | Failed at least two adequate duration and dose of antipsychotics other than CLZ; plus on CLZ (300–900 mg/d) at least 6 months; PANSS ≥ 72; CGI-S ≥ 4; a score of at least 3 on any 1 of PANSS-Positive subscale items (0–7 scale) were required for entry. |
| ASSION et al. (2008)[49] | Defined as partial or no response on a stable dose of CLZ for at least 3 months. |
| AZORIN et al. (2001)[60] | Patients were additionally required to meet the following minimum criteria for poor response to previous treatment. 1) The patient's current episode had been treated continually with a neuroleptic for at least the preceding 6 months without significant clinical improvement. 2) The patient had undergone one unsuccessful trial of antipsychotic medication equivalent to 20 mg/day of haloperidol for at least 6 weeks (less if the patient was experiencing dose-limiting adverse events) since the onset of the current episode. If several drugs had been prescribed simultaneously, the final equivalence dosage could be calculated by adding the individual equivalencies. 3) The patient had experienced no period of good functioning for at least 24 months despite a sufficient period of use of 2 antipsychotics from at least 2 chemical classes, or no period of good functioning for 5 years despite the use of 3 antipsychotics. Poor previous treatment response as defined in the current study differs from treatment resistance by having a less stringent criterion for the previous drug history than did the study by Kane et al.,[77] enabling patients to be more representative of those seen in current clinical practice compared with previous clinical trials. |
| BONDOLFI et al. (1998)[66] | Failed to respond to or were intolerant of at least 2 different classes of antipsychotic drugs given in appropriate doses for at least 4 weeks each. No subject had previously received clozapine. PANSS total score was 60–120. |
| CHANG et al. (2008)[38] | Treatment failure prior to CLZ treatment was defined as persistent psychotic symptoms despite at least 2 antipsychotic treatments for greater than 6 weeks at a full dose equivalent to 600 mg/d or more of chlopromazine. Treatment-resistant to CLZ was defined as: CLZ treatment for more than 1 year with at least 8 weeks at a stable daily dose of 400 mg or more, unless accompanied by adverse effects; no change in CLZ daily dose or other concomitant medication for more than 3 months, indicating a plateau of clinical response to CLZ; either BPRS total score of at least 35 or more than 2 SANS global rating items scores of at least 3. The minimum positive symptom total score of at least 8 on 4 items of the BPRS or a score of at least 4 on any one of the following items: hallucinatory behaviour, conceptual disorganization, unusual thought content, or suspiciousness. |
| CITROME et al. (2001)[59] | See companion publication: Volavka et al.[58] |

| Author (Year) | Definition of "Inadequate Response" for Inclusion in RCT |
|---|---|
| CLAUS et al. (1992)[68] | Despite optimization of conventional neuroleptic treatment, they still presented positive, negative, and/or EPS. |
| CONLEY et al. (1988)[65] | Initial screen stage: at least 2 periods of treatment in the preceding 5 years with an antipsychotic drug (from at least 2 different chemical classes, excluding haloperidol), at dosages ≥ 1,000 mg/day of chlorpromazine equivalents, for 6 weeks without significant symptomatic relief; 2) no period of good functioning within the past 5 years; and 3) severity of psychopathology indicated by a total score of 45 or more on the BPRS (items rated 1–7), a CGI severity score of 4 or more, and a score of 4 or more on at least 2 of the BPRS psychosis items (conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content). After the initial screening, subjects were given a prospective trial of haloperidol, 10–40 mg/day, and benztropine, 4 mg/day, for a period of 6 weeks. Haloperidol dosing was open and done by the treating psychiatrist. Failure to respond to the haloperidol trial was defined as less than a 20% decrease in total BPRS score, an endpoint BPRS score greater than 35, and a CGI severity score greater than 4 for patients completing at least 2 weeks of haloperidol therapy. |
| CONLEY et al. (2003)[76] | NR. See companion publication: KELLY et al. (2003)[48] |
| CZOBOR et al. (2002)[71] | NR. See Companion publication: Volavka et al.[58] |
| FLEISCHHACKER et al. (2010)[54] | DSM-IV-TR criteria for schizophrenia, less than optimal control was defined as residual positive, negative or other symptoms, as well as safety/tolerability problems such as somnolence, weight gain, prolactin elevation. Akathisia, or EPS. |
| FREUDENREICH et al. (2007)[41] | Patients had to failed at least two previous trials of antipsychotics prior to CLZ and currently treated with CLZ monotherapy for at least 6 months, at a stable dose for at least 8 weeks and with CLZ plasma levels of at least 200 ng/mL, unless intolerant. The subjects had schizophrenia as their primary diagnosis and displayed stable residual psychiatric symptoms as defined by a PANSS score greater than 60. |
| GENC et al. (2007)[50] | Partial response to at least a 12 week trial of 400 to 600 mg/d of clozapine (partial response was defined as persistent psychotic symptoms, as evidenced by a total score > 45 on the BPRS (on which each of 18 items is scored from 1 to 7) or a rating of moderately ill (> 4) on at least 2 of the 4 BPRS positive<br>symptom items (hallucinatory behaviour, conceptual disorganization, unusual thought content, and suspiciousness). |
| GREEN at al. (1997)[67] | Treatment-resistant was defined by Kane et al.[77] as at least three 6-week treatment periods with neuroleptics from at least 2 different classes (at doss of at least 1,000 mg/day of chlorpromazine equivalents) in the past 5 years that resulted in either no significant symptomatic relief or an inability to tolerate such doses. Absence of significant symptomatic relief defined as either no or only slight improvement that did not alter need for care of patient. |
| HONER et al. (2006)[44] | Treatment with clozapine for the indication of poor response to other antipsychotic agents; treatment for at least 12 weeks at a stable dose of 400 mg or more per day, unless the size of the dose was limited by side effects; a total score of 80 or greater at baseline on the Positive and Negative Syndrome Scale (PANSS); a CGI score of 4 or greater; and a Social and Occupational Functioning Assessment Scale (SOFAS)18 score of 40 or less |

| Author (Year) | Definition of "Inadequate Response" for Inclusion in RCT |
|---|---|
| HONER et al. (2011)[72] | Persistent positive (a total score ≥ 15 on PANSS positive subscale) with a score ≥ 4 on at least one of: delusions, conceptual disorganization, hallucinations, or suspiciousness) and/or negative (a total score ≥15 on PANSS negative subscale) with a score ≥ 4 on at least one of: blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, or lack of spontaneity) symptoms, and with a CGI score of at least 4, without a 30% or greater improvement in PANSS score during the 4 week open-label 800 mg quetiapine phase. |
| JOSIASSEN et al. (2005)[46] | Prior to treatment with clozapine, documented treatment failure after 2 antipsychotics approved by FDA for an adequate duration in a sufficient dose (6 or more weeks of 1,000 mg/day of chlorpromazine equivalents); in addition, demonstrated a documented failure to show a satisfactory clinical response to an adequate trial of clozapine (3 or more months of at least 600 mg/day of oral clozapine or a plasma drug level of 350 ng/mL or higher); and had persistent psychotic symptoms, as evidenced by either a total score of at least 45 on the BPRS (on which each of 18 items is scored from 1 to 7) or a rating of moderately ill (4 or more) on at least 2 of the 4 BPRS positive symptom items (hallucinatory behaviour, conceptual disorganization, unusual thought content, and suspiciousness). |
| KANE et al. (2009)[36] | Currently receiving a stable dose of quetiapine (400–800 mg/d) or risperidone (4–8 mg/d) for ≥ 4 weeks but with an inadequate response, which was primarily defined by investigators' judgment as a CGI-S score of 4 to 6. |
| KELLY et al. (2003)[48] | 1) Persistent positive psychotic symptoms: item score ≥ 4 (moderate) on at least 2 of 4 positive symptom items on BPRS; 2) the current presence of at least moderately severe illness as rated by the total BPRS score (score ≥ 45 on the 18-item scale) and a score of ≥ 4 (moderate) on the CGI; 3) two failed historical trials of antipsychotics of at least 6 weeks' duration at doses of at least 600 mg/day chlorpromazine equivalents; and 4) no stable period of good social and/or occupational functioning within the last 5 years. |
| KELLY et al. (2006)[43] | Persistent positive psychotic symptoms (item score ≥ 4 [moderate]) on at least 2-4 positive symptom items on BPRS; at least moderately severe illness at study entrance as rated by ≥ 45 on the total BPRS score (18-item scale) and a score of ≥ 4 (moderately ill) on the CGI; documentation of prior failed trials on two different antipsychotics of at least 6 weeks' duration at doses of at least 600 mg/day chlorpromazine equivalents; no period of good social and/or occupational functioning within the last 5 years. |
| KERN et al. (1998)[64] | NR. See companion publication: Green et al.[67] |
| KERN et al. (1999)[62] | NR. See companion publication: Green et al.[67] |
| KOTLER et al. (2004)[47] | All subjects met parameters for treatment-resistance following the criteria of Kane et al. (1988)[77] |
| KUMRA et al. (2008)[40] | Subjects also had to meet study criteria for treatment-refractoriness that was defined as a documented treatment failure of at least two prior adequate antipsychotic trials and a baseline BPRS, total score of at least 35, and a score of at least "moderate" on one or more psychotic item(s) on the BPRS (e.g., conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content). |

| Author (Year) | Definition of "Inadequate Response" for Inclusion in RCT |
|---|---|
| KUWILSKY et al. (2010)[55] | See companion publication: ZINK et al. (2009)[37] |
| LINDENMAYER et al. (2003)[57] | See Companion publication: Volavka et al.[58] |
| McEVOY et al. (2006)[70] | NR. Detail was reported in the CATIE study protocol.[327] No definition of inadequately response was provided in the protocol either. It was indicated that patients with inadequate resolution of psychopathology, or marked sensitivity to EPS (following a non-CLZ AAP treatment in phase 1) are recommended to enter this study (phase 2 study). |
| MELTZER et al. (2008)[39] | Treatment-resistant schizophrenia was defined based on the criteria of Kane et al. (1988).[77] Specifically, patients indicated moderate to severe levels (a score ≥ 4) for at least 2 of 4 the following types of positive symptoms — delusions, hallucinations, conceptual disorganizations, and unusual thought content — despite 2 or more trials of typical or atypical antipsychotic drugs from different classes, with usually adequate dose for at least 6 weeks. |
| MILLAR et al. (2008)[74] | Suboptimally controlled on a stable dose of CLZ for at least 3 months. |
| MOSSAHEB et al. (2006)[73] | Resistant to 2 adequate trials of 2 different classes of APDs and to a trial with CLZ in an adequate dosage for ≥ 6–8 weeks. |
| RICHARDSON et al. (2009)[75] | Incomplete response to CLZ in treatment-resistant schizophrenia; DSM-IV schizophrenia or schizoaffective disorders who continued to manifest moderate illness severity (18 items BPRS total ≥ 45 and CGI-S ≥ 4 and persistent psychosis (four psychosis item total ≥ 8, with one of these items ≥ 4) despite adequate prior CLZ treatment. |
| ROSENHECK et al. (1999)[63] | Criteria defined by Kane et al. (1988);[77] also defined as persisting psychotic symptoms despite 2 documented adequate treatment trials. |
| SHAFTI (2009)[52] | Poor response to clozapine was defined as < 25% decrement in total SAPS score on the treatment maximum dose of clozapine (25 mg/d) for at least 4 weeks; > 70 SAPS score at baseline. |
| SHILOH et al. (1997)[51] | Partial and unsatisfactory response to clozapine following at least 12 weeks of treatment in an adequate dose. Partial/unsatisfactory response to clozapine was defined as a score of at least 25 on the BPRS $_{0\text{-}6,}$ Overall & Gorham,1961) and inability to function as an outpatient. |

| Author (Year) | Definition of "Inadequate Response" for Inclusion in RCT |
|---|---|
| TOLLEFSON et al. (2001)[53] | All patients were required to have documented history that they were clinically resistant to previous APD treatments. Lack of clinical response to at least 2 previous oral neuroleptic treatments, each of a different chemical class, given for at least 6 weeks up to the maximum dose. |
| VOLAVKA et al. (2002)[58] | Suboptimal response to previous treatment, which was defined by 2 criteria that needed to be present. The first criterion of suboptimal response was persistent positive symptoms (hallucinations, delusions, or marked thought disorder) after at least 6 contiguous weeks of treatment, presently or documented in the past, with one or more typical antipsychotics at doses ≥ 600 mg/day in chlorpromazine equivalents. The second criterion was a poor level of functioning over the past 2 years, defined by the lack of competitive employment or enrolment in an academic or vocational program and not having age-expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained. |
| VOLAVKA et al. (2004)[56] | See Volavka et al. (2002)[58] |
| WEINER et al. (2010)[69] | BPRS total score ≥ 45 or CGI-S ≥ 4, and BPRS positive score ≥ 8, with one or more item rated ≥ 4. Adequate trial of clozapine, where clozapine treatment was ≥ 6 months on a dose producing clozapine plasma level ≥ 350 mg/mL or clozapine+norclozapine plasma level ≥ 450 ng/mL. |
| WIRSHING et al. (1999)[61] | Criteria defined by Kane et al. (1988):[77] a total BPRS score of at least 45, a minimum CGI scale rating of 4, a failure to respond to or an inability to tolerate at least three 6-week epochs of treatment within the preceding 5 years with AP meds from at least two different classes. |
| ZINK et al. (2009)[37] | Insufficient treatment response to clozapine monotherapy was assumed after a compliant treatment with ≥ 300 mg of clozapine per day over a period of ≥ 3 months with serum levels of ≥ 200 mcg/L or severe dose-limiting side effects of clozapine after shorter application or in lower doses. Treatment-resistant symptoms were reflected in a PANSS total score of ≥ 65. |

# APPENDIX 11: DEFINITION OF RESPONSE TO ANTIPSYCHOTIC DRUG TREATMENT REPORTED IN INCLUDED RCTS

| Author (Year) | Definition of Response |
|---|---|
| AKDEDE et al. (2005)[42] | 20% improvement in PANSS-T |
| ANIL YAGCIOGLU et al. (2005)[45] | 20% improvement in PANSS-T |
| ASSION et al. (2008)[49] | NR |
| AZORIN et al. (2001)[60] | 20% BPRS reduction plus CGI score ≤ 3 or end point CGI ≤ 3.5 |
| BONDOLFI et al. (1998)[66] | PANSS total score reduced by 20% or more from baseline |
| CHANG et al. (2008)[38] | NR |
| CITROME et al. (2001)[59] | NR |
| CLAUS et al. (1992)[68] | PANSS total score reduced by 20% or more from baseline |
| CONLEY et al. (1988)[65] | 20% improvement in BPRS total score |
| CONLEY et al. (2003)[76] | 20% drop in BPRS score |
| CZOBOR et al. (2002)[71] | NR |
| FLEISCHHACKER et al. (2010)[54] | An improvement of ≥ 30% from baseline in PANSS total score |
| FREUDENREICH et al. (2007)[41] | PANSS total improves by ≥ 20% |
| GENC et al. (2007)[50] | NR |
| GREEN at al. (1997)[67] | NR |
| HONER et al. (2006)[44] | Treatment response was defined as those with a decrease in total PANSS score of at least 20% |
| HONER et al. (2011)[72] | 20% or greater improvement in total PANSS score |
| JOSIASSEN et al. (2005)[46] | 20% reduction in BPRS total score at the end |
| KANE et al. (2009)[36] | ≥ 20% decrease from baseline in PANSS-T or CGI-I score of 1 or 2 |
| KELLY et al. (2003)[48] | NR |
| KELLY et al. (2006)[43] | NR |
| KERN et al. (1998)[64] | NR |
| KERN et al. (1999)[62] | NR |
| KOTLER et al. (2004)[47] | NR |

| Author (Year) | Definition of Response |
|---|---|
| KUMRA et al. (2008)[40] | To reflect a clinically meaningful improvement the primary protocol efficacy measure as categorical response, which was defined as a decrease of 30% or more in total BPRS score from the baseline to endpoint and a Clinical Global Impression Scale improvement rating of “1” (very much improved) or “2” (much improved). |
| KUWILSKY et al. (2010)[55] | see ZINK et al. (2009)[37] |
| LINDENMAYER et al. (2003)[57] | NR |
| McEVOY et al. (2006)[70] | NR |
| MELTZER et al. (2008)[39] | ≥ 20% decrease from baseline in PANSS-T at 6 months for completers and at 6 wks for those who dropped out after wk 6 for reasons other than lack of efficacy |
| MILLAR et al. (2008)[74] | NR |
| MOSSAHEB et al. (2006)[73] | NR |
| RICHARDSON et al. (2009)[75] | NR |
| ROSENHECK et al. (1999)[63] | 20% improvement on either PANSS or the Heinrichs-Carpenter Quality of Life Scale |
| SHAFTI, (2009)[52] | NR |
| SHILOH et al. (1997)[51] | A reduction of more than 20% in the BPRS scores |
| TOLLEFSON et al. (2001)[53] | Achieved ≥20% reduction in BPRS, total score from baseline to endpoint, plus either an endpoint CGI-S score of ≤ 3 or an endpoint BPRS total score of ≤ 3.5 |
| VOLAVKA et al. (2002)[58] | NR |
| VOLAVKA et al. (2004)[56] | NR |
| WEINER et al. (2010)[69] | NR |
| WIRSHING et al. (1999)[61] | 20% or more improvement in BPRS scores at the end of the flexible phase and CGI at most less than 3 mild or a total score of 3.5 or less on the 18-items BPRS |
| ZINK et al. (2009)[37] | Reduction of the PANSS by 20% or reduction of PANSS-positive by 20% |

# APPENDIX 12: STUDY CHARACTERISTICS OF INCLUDED STUDIES

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| AKDEDE et al. (2005)[42] | Turkey | Grant from Stanley Medical research Institute, Janssen Pharmaceutica, THE Ritter Foundation, the William K. Warren Medical Research Foundation | RIS+CLZ<br>515.6±138.7 mg/d CLZ and<br>5.1±1.3 mg/day RIS<br>PLC+CLZ<br>414.3±96.9 mg/d CLZ | Benzodiazepines for anxiety and/or biperiden for EPS allowed if necessary | 6 weeks | ≥3 | 30 |
| ANIL YAGCIOGLU et al. (2005)[45] | See Akdede 2006 | | | | | | |
| ASSION et al. (2008)[49] | Germany | Sanofi-Synthelabo | AMI400+CLZ<br>400mg/d AMI and 300 mg/d CLZ<br>AMI600+CLZ<br>600 mg/d AMI and 300mg/d CLZ<br>PLC+CLZ<br>300 mg/d CLZ | Occasional intake of benzodiazepines, sedatives, or antidepressants allowed | 6 weeks | ≥1 | 16 |
| AZORIN et al. (2001)[60] | France and Canada | Novartis Phama S.A. | RIS (H): median 9 mg/d<br>CLZ: median: 600 mg/d | Not reported | 12 weeks | ≥1 | 273 |
| BONDOLFI et al. (1998)[66] | France and Switzerland | Janssen Research Foundation | RIS (H): 6.4 mg/d<br>CLZ: 291.2 mg/d | Lorazepam or oxazepam for sleep induction or daytime sedation; | 8 weeks | ≥2 | 86 |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| | | | | biperiden and procyclidine for EPS | | | |
| CHANG et al. (2008)[38] | Korea | Supported by grants from Brain Research center, funded by the Ministry of Science and Technology; Republic of Korea and Otsuka Pharmaceutical | ARI+CLZ<br>15.5±7.1 mg/d ARI and 400 mg/d CLZ<br>PLC+CLZ<br>400mg/d CLZ | Antidepressants, anticholinergics and benzodiazepine | 8 weeks | ≥3 | 62 |
| CITROME et al. (2001)[59] | See Volavka 2002[58] | | | | | | |
| CLAUS et al. (1992)[68] | Belgium | Janssen Research Foundation | RIS (H): 12 mg/d<br>Hal: 10 mg/d | Diazepam allowed for sedation; Dexetimide allowed for EPS; Etybenzatropine for acute dystonia | 12 weeks | Not reported | 44 |
| CONLEY et al. (1998)[65] | USA | Supported by NIMH grants. Eli Lilly provided investigational drugs | OLZ+PLC: 25 mg/d<br>CPZ+Benz:<br>1200 mg/d chlorpromazine and 4 mg/d benztropine mesylate | Benztropine mesylate (chlorpromazine group), or placebo (olanzapine | 6 weeks | ≥3 | 84 |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| | | | | group). Lorazepam (up to 8 mg/day) for agitation or anxiety. No other centrally acting medications. | | | |
| CONLEY et al. (2003)[76] | USA | NIMH and Intervention Research Center grants | OLZ (H): 50 mg/d<br>CLZ: 450 mg/d | lorazepam or benztropine mesylate | 8 weeks (pre-crossover) | ≥2 | 13 |
| CZOBOR et al. (2002)[71] | See Volavka 2002[58] | | | | | | |
| FLEISCHHACKER et al. (2010)[54] | Austria | Bristol-Meyers Squibb | ARI+CLZ<br>11.1 mg/d ARI and 383.8±158.2 mg/d CLZ<br>PLC+CLZ<br>12.0 mg/day PLC and 362.6.8±158.7 mg/d CLZ | Benzodiazepines and anticholinergics, sleep aids for insomnia, anti-depressants and mood stabilizers at a stable dose if the patient taking prior to study entry. Propranolol for akathisia. | 16 weeks | Not reported | 207 |
| FREUDENREICH et al. (2007)[41] | USA | Stanley Medical Research Institute | RIS+CLZ<br>4 mg/d RIS and 456 mg/d CLZ<br>PLC+CLZ<br>456 mg/d CLZ | stable psychotropics | 6 weeks | ≥2 | 24 |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| GENC et al. (2007)[50] | Turkey | Not reported | AMI+CLZ<br>437±104 mg/d AMI and 536–550 mg/d CLZ<br>QUET+CLZ<br>596±125.25 mg/d QUET and 536–550 mg/d CLZ | Not reported | 8 weeks | ≥1 | 56 |
| GREEN at al. (1997)[67]† | See KERN et al. (1999)[62] | | | Lorazepam, propranolol, chloral hydrate, benztropine or biperiden | See KERN et al. (1999)[62] | | 59 analyzed |
| HONER et al. (2006)[44] | Multinational (Canada, China, Germany, UK) | Stanley medical research institute. Risperidone provided by Jansen-Ortho, Canada | RIS+CLZ<br>2.94±0.2 mg/d RIS and 492 mg/d±192 mg/d CLZ<br>PLC+CLZ<br>2.88±0.42 mg/d PLC and 492 mg/d±131 mg/d CLZ | Lorazepam or chloral hydrate for treatment of agitation or other symptoms, not within 48 hours of cognitive tests. Anticholinergics for acute side effects. | 8 weeks | Not reported | 68 |
| HONER et al. (2011)[72] | Canada | Astra Zeneca | QUET (H): 1,144 mg/d<br>QUET: 799 mg/d | antidepressants, mood stabilizers or hypnotics if stable dose for 30 days prior to entry. Flurazepam or zaleplon for sleep, lorazepam | 8 weeks | ≥1 | 131 |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| | | | | for agitation. Anticholinergic medication for treatment-emergent EPS | | | |
| JOSIASSEN et al. (2005)[46] | USA | Johnson & Johnson Pharmaceutical Research & Development | RIS+CLZ<br>4.43±1.5 mg/d RIS and ≥600 mg/d CLZ<br>PLC+CLZ<br>≥600 mg/d CLZ | Not reported | 12 weeks | ≥3 | 40 |
| KANE et al. (2009)[36] | USA | Bristol-Meyers Squibb, USA and Otsuka Pharmaceutical Co Ltd, Japan | ARI + (RIS or QUET)<br>10.3 mg/d ARI and 513 mg/d QUET or 4.6 mg/d RIS<br>PLC + (RIS or QUET)<br>516 mg/d QUET or 4.8 mg/d RIS | Antidepressants (not fluoxetine or paroxetine); anticholinergics; mood stabilizers; anticonvulsants (not carbamazepine); and benzodiazepines if pts receiving stable dose for ≥ 4 weeks prior to study entry. Benzodiazepine for manage treatment-emergent agitation or anxiety. | 16 weeks | ≥1 | 323 |
| KELLY et al. (2003)[48] | See Conley 2003[76] | | | | | | |
| KELLY et al. (2006)[43] | See Conley 2003[76] | | | | | | |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| KERN et al. (1998)[64]† | See KERN et al. (1999)[62] | | | | | | 56 analyzed |
| KERN et al. (1999)[62]† | USA | NIMH UCLA Research Center for the Study of Schizophrenia, Janssen Research Foundation, Department of Veterans Affairs | RIS (H): 7mg/d<br>Hal: 19 mg/d | Lorazepam, propranolol, chloral hydrate, benztropine or biperiden (See GREEN at al. (1997)[67]) | 8 weeks | ≥2 classes | 64 analyzed |
| KOTLER et al. (2004)[47] | Israel | Not reported | Sulpiride+OLZ(H):<br>up to 600 mg/d Sul and 22.4±4.37 mg/d OLZ<br>OLZ(H):<br>22.4±4.37 mg/d OLZ (no placebo) | None | 8 weeks | ≥1 | 17 |
| KUMRA et al. (2008)[40] | USA | Not reported | OLZ (H): 26.2 ± 6.5 mg/d<br>CLZ: 403.1 ± 201.8 mg/d | Lithium, depakote, other mood stabilizers, antidepressants, stimulants, and naltrexone. 3 subjects could not be tapered off previous APD. | 12 weeks | ≥2 | 39 |
| KUWILSKY et al. (2010)[55]† | See Zink 2009[37] | | RIS+CLZ<br>2.75±1.3 mg/d RIS and 450.0±168.3 mg/d CLZ<br>ZIP+CLZ | See Zink 2009[37] | 52 weeks | See Zink 2009[37] | |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| | | | 120±65.3 mg/d ZIP and 325.0±185.4 mg/d CLZ | | | | |
| LINDENMAYER et al. (2003)[57]† | See Volavka, 2002[58] | | OLZ (H): 31.4±6.0 mg/d<br>RIS (H): 11.6±3.7 mg/d<br>CLZ: 477.2±157.2 mg/d<br>Hal: 25.8±5.1 mg/d | See Volavka 2002[58] | | | 101 analyzed |
| McEVOY et al. (2006)[70] | USA | NIMH, IVAX corporation | OLZ(H): mean modal 23.4 mg/d<br>CLZ: mean modal 332.1 mg/d | Non-APD meds permitted | 24 weeks | ≥1 | 68 |
| MELTZER et al. (2008)[39] | USA | Eli Lilly and other foundations | OLZ(H): 33.6±11.2 mg/d<br>CLZ: 564±243 | Anti-depressants | 26 weeks | ≥2 | 40 |
| MILLAR et al. (2008)[74] | Not reported | funded by Bristol-Myers Squibb and Otsuka | ARI+CLZ: 4 to 15mg/d ARI, CLZ dose not reported<br>PLC+CLZ: CLZ dose not reported | Not reported | 16 weeks | ≥1 | 207 |
| MOSSAHEB et al. (2006)[73] | Austria | Not reported | Hal+CLZ<br>4 mg/d Hal and 450±70.7 mg/d CLZ<br>PLC+CLZ<br>500±81.7 mg/d CLZ | Not reported | 10 weeks | ≥3 | 10 |
| RICHARDSON et al. (2009)[75] | USA | Lilly Pharmaceuticals | RIS+CLZ: 4 mg/d RIS; CLZ dose not reported<br>PLC+CLZ: CLZ dose not reported | Not reported | 16 weeks | ≥1 | 65 |
| ROSENHECK et al. (1999)[63] | USA | Dept. Veterans Affairs Health | CLZ(H): 628 mg/d<br>Hal: 28.2 mg/d | benztropine mesylate | 52 weeks | ≥2 | 245 |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| | | Services R&D, Sandoz Pharm. Co. | | | | | |
| SHAFTI (2009)[52] | Iran | Not reported | Fluphenazine+OLZ(H) 17.42±6.07 mg/2 wks FLU and 21.96±5.03 mg/d OLZ<br>PLC+OLZ(H): 21.96±5.03 mg/d OLZ | None | 12 weeks | ≥1 | 28 |
| SHILOH et al. (1997)[51] | Israel | Not reported | SUL+CLZ<br>600 mg/d SUL and 403.1±137.2 mg/d CLZ<br>PLC+CLZ<br>445.8±132.2 mg/d CLZ | None | 10 weeks | ≥3 | 28 |
| TOLLEFSON et al. (2001)[53] | Multinational (Europe and South Africa) | Eli Lilly | OLZ(H): 20.5 ± 2.8 mg/d<br>CLZ: 303.6 ± 108.7 mg/d | Benzodiazepine, chloral hydrate, biperiden or benztropine mesylate | 18 weeks | ≥2 | 180 |
| VOLAVKA et al. (2002)[58] | USA | NIMH grant; pharmaceutical companies provided drugs | OLZ (H): 30.4±6.6 mg/d<br>RIS (H): 11.6±3.2 mg/d<br>CLZ: 526.6±140.3 mg/d<br>Hal: 25.7±5.7 mg/d | Benztropine, lorazepam, diphenhydramine hydrochloride, or chloral hydrate were allowed. No other mood stabilizers or antidepressants allowed | 14 weeks | ≥1 | 167 analyzed |

| Author, Year | Country | Sponsor | Interventions/ Comparators (Mean Dose) | Adjunctive Medications Allowed | Treatment Duration (Weeks) | Number of APDs Failed Prior to Study | Sample Size |
|---|---|---|---|---|---|---|---|
| VOLAVKA et al. 2004[56] | See Volavka 2002[58] | | | | | | |
| WEINER et al. (2010)[69] | USA | NIMH and U. of Maryland | RIS+CLZ<br>4 mg/d RIS and CLZ level 680.1±446.6 ng/mL<br>PLC+CLZ<br>CLZ level 491.2±264.0 ng/mL | Not reported | 16 weeks | ≥1 | 69 |
| WIRSHING et al. (1999)[61] | See Kern 1999[62] | | RIS (H): 7.5 ± 1.9 mg/d<br>Hal: 19.4 ± 5.6 mg/d | Anticholinergics (benztropine or biperiden), propranolol, lorazepam, temazepam | See Kern 1999[62] | | 67 |
| ZINK et al. (2009)[37]† | Germany | Pfizer Pharma GmbH and other author grants | RIS+CLZ<br>3.82 ± 1.8 mg/d RIS and 437.5±140.4 mg/d CLZ<br>ZIP+CLZ<br>134±34.4 mg/d ZIP and 370.8±150.0 mg/d CLZ | Valproic acid, antidepressants, benzodiazepine, clonazepam | 6 weeks | ≥2 | 24 |

† Several trials were reported in multiple publications; however, the number of patients included in analyses or the time point reported was different between publications.

# APPENDIX 13: PATIENT CHARACTERISTICS OF INCLUDED STUDIES

| Author, Year | Avg. Age (Years) | % Male | Avg. Duration of SZ/SAD (Years) | Baseline PANSS/BPRS Score |
|---|---|---|---|---|
| AKDEDE et al. (2005)[42] | RIS+CLZ: 35.3 (SD: 10.8)<br>PLC+CLZ: 31.2 (SD: 6.9) | RIS+CLZ: 56%<br>PLC+CLZ: 79% | RIS+CLZ: 14.4 (SD: 9.1)<br>PLC+CLZ: 9.8 (SD: 5.9) | PANSS<br>RIS+CLZ: 77.4 (SE:1.65)<br>PLC+CLZ: 77.4 (SE:1.78) |
| ANIL YAGCIOGLU et al. (2005)[45] | See Akdede 2006[42] | | | |
| ASSION et al. (2008)[49] | AMI600+CLZ: 41.5<br>AMI400+CLZ: 43.0<br>PLC+CLZ: 46.3 | AMI600+CLZ: 50%<br>AMI400+CLZ: 85.7%<br>PLC+CLZ: 100% | Not reported | Not reported |
| AZORIN et al. (2001)[60] | RIS (H):39.5 (SD: 11.2)<br>CLZ: 38.3 (SD: 10.2) | RIS (H): 65.5%<br>CLZ: 78.5% | RIS (H): 15.5<br>CLZ: 14.0 | BPRS<br>RIS (H): 60.8 (SD: 9.7)<br>CLZ: 64.0 (SD: 9.9) |
| BONDOLFI et al. (1998)[66] | RIS (H): 38.3 (SD: 12.9)<br>CLZ: 36.2 (SD: 12.2) | RIS (H): 67.4%<br>CLZ: 74.4% | Not reported | PANSS<br>RIS (H): 106.3 (SD: 11.7)<br>CLZ: 100.4 (SD: 15.2) |
| CHANG et al. (2008)[38] | ARI+CLZ : 33.2 (SD: 8.2)<br>PLC+CLZ : 31.7 (SD: 7.4) | ARI+CLZ : 76%<br>PLC+CLZ : 81.3% | ARI+CLZ : 13<br>PLC+CLZ : 12 | BPRS<br>ARI+CLZ : 47.6 (SD: 9.3)<br>PLC+CLZ : 48.5 (SD: 10.5) |
| CITROME et al. (2001)[59] | See Volavka 2002[58] | | | |
| CLAUS et al. (1992)[68] | RIS (H): 37.4<br>Hal: 39.0 | RIS (H): 71.4%<br>Hal: 61.9% | RIS (H) : ~14.6<br>Hal :~13.6<br>Note: Approximated from mean age and mean age at onset | PANSS<br>RIS (H): 91.1 (SE: 4.1)<br>Hal: 79.8 (SE: 5.7) |
| CONLEY et al. (1998)[65] | 42.77±9.74 | 73.8% | 21.31±8.10 | BPRS<br>OLZ+PLC : 57.2 (SD: 8.4)<br>CPZ+Benz :57.8 (SD: 8.6) |
| CONLEY et al. (2003)[76] | OLZ (H) : 35.91 (SD: 9.02)<br>CLZ : 40.26 (SD: 8.87) | OLZ (H) : 50%<br>CLZ : 80% | OLZ (H) : ~13.4<br>CLZ : ~22.0<br>Note: Approximated | BPRS<br>OLZ (H) : 58.0 (SD: 7.7)<br>CLZ : 59.4 (SD: |

| Author, Year | Avg. Age (Years) | % Male | Avg. Duration of SZ/SAD (Years) | Baseline PANSS/BPRS Score |
|---|---|---|---|---|
| | | | from mean age and mean age at onset | 8.2) |
| CZOBOR et al. (2002)[71] | See Volavka 2002[58] | | | |
| FLEISCHHACKER et al. (2010)[54] | ARI+CLZ : 37.6 (SD: 10.9) PLC+CLZ : 40.5 (SD: 9.98) | ARI+CLZ : 63% PLC+CLZ : 67% | ARI+CLZ : 12.6 (SD: 9.3) PLC+CLZ : 14.4 (SD: 9.1) | PANSS ARI+CLZ : 72.2 (SD: 16.6) PLC+CLZ : 70.7 (SD: 16.5) |
| FREUDENREICH et al. (2007)[41] | 42.3 | 87.5% | 20.6 | PANSS RIS+CLZ : 72.4 (SD: 11.9) PLC+CLZ : 73.5 (SD: 11.0) |
| GENC et al. (2007)[50] | AMI+CLZ: 37.29 (SD: 8.17) QUET+CLZ : 37.30 (SD : 8.18) | AMI+CLZ: 43% QUET+CLZ: 32% | AMI+CLZ: 15.66 (SD: 6.98) QUET+CLZ : 15.69 (SD : 6.90) | BPRS AMI+CLZ: 50.55 (SD: 3.59) QUET+CLZ : 48.69 (SD : 3.00) |
| GREEN at al. (1997)[67] † | RIS (H): 41.47 (SD: 9.75) Hal: 39.86 (SD: 8.16) | RIS (H): 80% Hal: 86% | RIS (H): 19.73 (SD: 9.58) Hal: 18.71 (SD: 7.84) | Not reported; see Kern 1999[62] for approximation† |
| HONER et al. (2006)[44] | RIS+CLZ: 39.4 (SD: 11.0) PLC+CLZ: 34.9 (SD: 8.5) | RIS+CLZ : 74% PLC+CLZ : 74% | RIS+CLZ: 16.9 (SD: 11.2) PLC+CLZ: 13.0 (SD: 9.0) | PANSS RIS+CLZ: 102.5 (SD: 14.6) PLC+CLZ: 97.8 (SD: 12.4) |
| HONER et al. (2011)[72] | QUET (H): 40.6 (SD: 12.5) QUET: 37.9 (SD: 10.9) | QUET (H) : 66% QUET : 74% | Not reported | PANSS QUET (H): 88.7 (SD: 10.7) QUET: 88.9 (SD: 10.4) |
| JOSIASSEN et al. (2005)[46] | RIS+CLZ: 40.8 (SD: 6.9) PLC+CLZ: 39.9 (SD: 10.8) | RIS+CLZ : 95% PLC+CLZ : 80% | RIS+CLZ: 21.8 (SD: 7.0) PLC+CLZ: 22.4 (SD: 11.6) | BPRS RIS+CLZ: 48.8 (SD: 9.2) PLC+CLZ: 47.1 (SD: 13.3) |
| KANE et al. (2009)[36] | ARI+(RIS or QUET) : 44.1 (SD : 11.3) PLC+(RIS or QUET) : 44.4 (SD : 12.0) | ARI+(RIS or QUET) : 58.9% PLC+(RIS or QUET) : 63.9% | Not reported | PANSS ARI+(RIS or QUET) : 74.5 (SD : 13.3) PLC+(RIS or QUET) : 75.9 (SD : 13.3) |
| KELLY et al. (2003)[48] | See Conley 2003[76] | | | |
| KELLY et al. (2006)[43] | See Conley 2003[76] | | | |
| KERN et al. | RIS (H): 40.8 | | RIS (H): 19.2 | BPRS |

| Author, Year | Avg. Age (Years) | % Male | Avg. Duration of SZ/SAD (Years) | Baseline PANSS/BPRS Score |
|---|---|---|---|---|
| (1998)[64]† | (SD: 10.2)<br>Hal: 39.6 (SD: 7.8) | RIS (H): 74%<br>Hal: 86% | (SD: 10)<br>Hal: 18.5 (SD: 7.9) | RIS (H): 63.8 (SD: 10.6)<br>Hal: 67.8 (SD: 12.0) |
| KERN et al. (1999)[62]† | RIS (H): 41.5 (SD: 9.5)<br>Hal: 39.8 (SD: 8.4) | RIS (H): 78%<br>Hal: 88% | RIS (H): 19.8 (SD: 9.5)<br>Hal: 18.3 (SD: 7.8) | BPRS<br>RIS (H): 64.0 (SD: 11.2)<br>Hal: 65.8 (SD: 11.7) |
| KOTLER et al. (2004)[47] | Sul+OLZ(H): 34.5 (SD:9.2)<br>OLZ(H): 27.6 (SD:4.6) | Sul+OLZ(H): 44%<br>OLZ(H):63% | Sul+OLZ(H): 13.4 (SD:9.5)<br>OLZ(H): 9.0 (SD:4.4) | PANSS<br>Sul+OLZ(H):104.1 (SD:21.0)<br>OLZ(H):103 (SD:15.6) |
| KUMRA et al. (2008)[40] | OLZ(H): 15.5 (SD: 2.1)<br>CLZ: 15.8 (SD: 2.2) | OLZ(H): 61.9%<br>CLZ: 44.4% | OLZ (H) : ~4<br>CLZ :~3<br>Note: Approximated from mean age and mean age at onset | BPRS<br>OLZ(H): 52.9 (SD: 10.4)<br>CLZ: 53.3 (SD: 12.0) |
| KUWILSKY et al. (2010)[55]† | See Zink 2009[37] | | | |
| LINDENMAYER et al. (2003)[57]† | Not reported; see Volavka 2002[56] for approximation† | 84.2% | Not reported; see Volavka 2002[56] for approximation† | Not reported; see Volavka 2002[56] for approximation† |
| McEVOY et al. (2006)[70] | OLZ(H): 44.3 (SD: 10.5)<br>CLZ: 39.4 (SD: 9.9) | OLZ(H): 95%<br>CLZ: 82% | OLZ (H) : ~18<br>CLZ :~18<br>Note: Approximated from mean age and mean age at onset | PANSS<br>OLZ(H): 83.1 (SD: 19.1)<br>CLZ: 90.3 (SD: 21.3) |
| MELTZER et al. (2008)[39] | OLZ(H): 36.4 (SD: 11.1)<br>CLZ: 37.2 (SD : 9.2) | OLZ(H): 63%<br>CLZ: 71% | OLZ(H): 16.6 (SD: 12.7)<br>CLZ: 14.7 (SD: 7.8) | PANSS<br>OLZ(H): 92.2 (SE: 2.4)<br>CLZ: 91.9 (SE : 2.3) |
| MILLAR et al. (2008)[74] | Not reported | | | |
| MOSSAHEB et al. (2006)[73] | 32.5 | Not reported | Not reported | PANSS<br>Hal+CLZ: 86.0 (SD: 4.2)<br>PLC+CLZ: 96.2 (SD: 30.3) |
| RICHARDSON et al. (2009)[75] | RIS+CLZ: 48.3 (SD: 7.2)<br>PLC+CLZ: 43.6 (SD: 9.6) | RIS+CLZ: 63.3%<br>PLC+CLZ: 71.4% | Not reported | BPRS ≥ 45.0 |
| ROSENHECK et | CLZ(H): 43.31 | CLZ(H): | CLZ (H) : ~21 | PANSS |

| Author, Year | Avg. Age (Years) | % Male | Avg. Duration of SZ/SAD (Years) | Baseline PANSS/BPRS Score |
|---|---|---|---|---|
| al. (1999)[63] | (SD:7.1)<br>Hal: 44.46 (SD: 8.4) | 99.2%<br>Hal: 99.1% | Hal :~22<br>Note: Approximated from mean age and mean age at onset | CLZ(H): 90.8 (SD:13.8)<br>Hal: 90.5 (SD: 13.3) |
| SHAFTI (2009)[52] | FLU+OLZ(H): 37.33 (SD:4.61)<br>PLC+OLZ(H): 35.78 (SD:5.58) | 0% | FLU+OLZ(H): 7.68 (SD:2.76)<br>PLC+OLZ(H): 6.73 (SD:2.12) | CGI-S<br>FLU+OLZ(H): 4.16(SD:0.39)<br>PLC+OLZ(H): 4.13 (SD:1.02) |
| SHILOH et al. (1997)[51] | SUL+CLZ: 40.3 (SD: 10.8)<br>PLC+CLZ: 37.1 (SD: 12.3) | SUL+CLZ: 68.8%<br>PLC+CLZ: 66.7% | SUL+CLZ: 20.5 (SD: 10.5)<br>PLC+CLZ: 19.3 (SD: 7.4) | BPRS<br>SUL+CLZ: 41.9 (SD: 12.2)<br>PLC+CLZ: 43.5 (SD: 9.7) |
| TOLLEFSON et al. (2001)[53] | 38.6 (SD:10.6) | 63.8% | Not reported | PANSS<br>OLZ(H): 108.2 (SD:15.7)<br>CLZ: 104.6 (SD: 20.0) |
| VOLAVKA et al. (2002)[58] | 40.8 (SD: 9.2) | 84.7% | 19.5 (SD:8.4) | PANSS<br>OLZ (H): 91 (SD:13.5)<br>RIS (H): 89.5 (SD: 13.8)<br>CLZ: 97.6 (SD: 17.1)<br>Hal: 90.4 (SD: 11.6) |
| VOLAVKA et al. (2004)[56] | See Volavka 2002[58] | | | |
| WEINER et al. (2010)[69] | RIS+CLZ: 48.3 (SD :7.2)<br>PLC+CLZ: 44.1 (SD :9.3) | RIS+CLZ: 63.3%<br>PLC+CLZ: 73.5% | RIS+CLZ : ~28<br>PLC+CLZ :~26<br>Note: Approximated from mean age and mean age at onset | BPRS<br>RIS+CLZ: 43.0 (SD :8.7)<br>PLC+CLZ: 44.4 (SD :9.2) |
| WIRSHING et al. (1999)[61]† | RIS (H): 41 .0 (SD: 9.4)<br>Hal: 40.0 (SD: 8.2) | RIS (H): 77%<br>Hal: 88% | RIS (H): 19.4 (SD: 9.3)<br>Hal: 18.7 (SD: 7.7) | BPRS<br>RIS (H): 66.8 (SD: 14.3)<br>Hal: 70.8 (SD: 14.6) |
| ZINK et al. (2009)[37]† | RIS+CLZ: 31.83 (SD:13.5)<br>ZIP+CLZ: 37.25 (SD:9.9) | RIS+CLZ: 58.3%<br>ZIP+CLZ: 58.3% | RIS+CLZ: 9.3 (SD:10.3)<br>ZIP+CLZ: 13.8 (SD:9.4) | PANSS<br>RIS+CLZ: 83.8 (SD:11.2)<br>ZIP+CLZ: 82.1 (SD:11.0) |

† Several trials were reported in multiple publications; however, the number of patients included in analyses or the time point reported were different between publications, thus some patient parameters differ.

# APPENDIX 14: QUALITY ASSESSMENT OF RCTS

| Study | Appropriate and Clearly Focused Question | Randomized Assignment | Adequate Concealment | Blinding of Subjects and Investigators | Groups are Similar at Baseline | Only Difference between Groups is Treatment under Investigation | Standard, Valid, and Reliable Measurement of Outcome(s) | Drop-out Rate is Acceptable (< 20%) and is Comparable between the Groups | ITT Analysis Performed | Comparable Results for Multi-Study Sites | Overall QA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AKDEDE et al. (2005)[42] | AA | NR | NAd | AA | PA | PA | AA | Yes | AA | NAd | Poor |
| ANIL YAGCIOGLU et al. (2005)[45] | AA | AA | NAd | AA | PA | AA | AA | Yes | AA | NAd | Poor |
| ASSION et al. (2008)[49] | AA | NR | NAd | PA | AA | AA | AA | No | NAd | NA | Poor |
| AZORIN et al. (2001)[60] | AA | NR | NAd | NR | PA | AA | AA | No | PA | PA | Poor |
| BONDOLFI et al. (1998)[66] | AA | NR | NAd | AA | AA | PA | PA | No | AA | NAd | Poor |
| CHANG et al. (2008)[38] | AA | WA | AA | WA | AA | AA | AA | Yes | AA | NA | Very good |
| CITROME et al. (2001)[59] | AA | NR | NAd | AA | AA | PA | AA | No | PA | NAd | Poor |
| CLAUS et al. (1992)[68] | AA | NR | NAd | NR | PA | PA | AA | No | AA | NAd | Poor |
| CONLEY et al. (1988)[65] | AA | NAd | NR | AA | AA | AA | AA | No | PA | AA | Poor |
| CONLEY et al. (2003)[76] | Letters to Editors; no QA was done. See companion publication KELLY et al. (2006)[43] | | | | | | | | | | |

| Study | Appropriate and Clearly Focused Question | Randomized Assignment | Adequate Concealment | Blinding of Subjects and Investigators | Groups are Similar at Baseline | Only Difference between Groups is Treatment under Investigation | Standard, Valid, and Reliable Measurement of Outcome(s) | Drop-out Rate is Acceptable (< 20%) and is Comparable between the Groups | ITT Analysis Performed | Comparable Results for Multi-Study Sites | Overall QA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CZOBOR et al. (2002)[71] | AA | NR | NAd | WA | PA | PA | AA | No | PA | NAd | Poor |
| FLEISCHHACKER et al. (2010)[54] | AA | WC | AA | NR | AA | AA | AA | Yes | AA | NAd | Good |
| FREUDENREICH et al. (2007)[41] | AA | NR | NAd | PA | AA | AA | AA | Yes | WC | NAd | Poor |
| GENC et al. (2007)[50] | AA | NR | NAd | AA | WC | AA | AA | Yes | PA | NA | Poor |
| GREEN at al. (1997)[67] | See companion publication: KERN et al. (1999)[62] | | | | | | | | | | |
| HONER et al. (2006)[44] | AA | WC | NAd | NR | AA | AA | AA | Yes | AA | PA | Good |
| HONER et al. (2011)[72] | WC | WC | AA | AA | PA | PA | AA | No | AA | NR | Poor |
| JOSIASSEN et al. (2005)[46] | WC | AA | NR | AA | AA | PA | PA | Yes | WC | NA | Poor |
| KANE et al. (2009)[36] | WC | AA | PA | PA | AA | PA | AA | No | AA | NR | Poor |
| KELLY et al. (2003)[48] | See companion publication: KELLY et al. (2006)[43] | | | | | | | | | | |
| KELLY et al. (2006)[43] | WC | NR | NAd | PA | AA | AA | AA | No | AA | NA | Poor |
| KERN et al. (1998)[64] | See companion publication: KERN et al. (1999)[62] | | | | | | | | | | |

| Study | Appropriate and Clearly Focused Question | Randomized Assignment | Adequate Concealment | Blinding of Subjects and Investigators | Groups are Similar at Baseline | Only Difference between Groups is Treatment under Investigation | Standard, Valid, and Reliable Measurement of Outcome(s) | Drop-out Rate is Acceptable (< 20%) and is Comparable between the Groups | ITT Analysis Performed | Comparable Results for Multi-Study Sites | Overall QA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| KERN et al. (1999)[62] | AA | NR | NAd | AA | AA | PA | PA | NR | NR | NAd | Poor |
| KOTLER et al. (2004)[47] | AA | NR | NAd | PA | PA | AA | AA | Yes | PA | NAd | Poor |
| KUMRA et al. (2008)[40] | WC | WC | AA | AA | AA | PA | AA | No | AA | PA | Poor |
| KUWILSKY et al. (2010)[55] | AA | WC | NAd | NAd | AA | PA | AA | No | PA | NAd | Poor |
| LINDENMAYER et al. (2003)[57] | AA | PA | NAd | AA | PA | PA | AA | No | PA | NAd | Poor |
| McEVOY et al. (2006)[70] | WC | NR | NAd | PA | AA | PA | AA | No | PA | NR | Poor |
| MELTZER et al. (2008)[39] | WC | AA | WC | WC | AA | AA | WC | No | PA | NAd | Poor |
| MILLAR et al. (2008)[74] | Abstract; no QA was done | | | | | | | | | | |
| MOSSAHEB et al. (2006)[73] | Abstract; no QA was done | | | | | | | | | | |
| RICHARDSON et al. (2009)[75] | Abstract; no QA was done | | | | | | | | | | |
| ROSENHECK et al. (1999)[63] | WC | NR | NAd | NR | AA | PA | AA | NR | PA | NAd | Poor |
| SHAFTI, (2009)[52] | WC | PA | NAd | AA | AA | AA | AA | Yes | WC | NAd | Poor |

| Study | Appropriate and Clearly Focused Question | Randomized Assignment | Adequate Concealment | Blinding of Subjects and Investigators | Groups are Similar at Baseline | Only Difference between Groups is Treatment under Investigation | Standard, Valid, and Reliable Measurement of Outcome(s) | Drop-out Rate is Acceptable (< 20%) and is Comparable between the Groups | ITT Analysis Performed | Comparable Results for Multi-Study Sites | Overall QA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SHILOH et al. (1997)[51] | WC | PA | NR | AA | AA | AA | AA | Yes | WC | NA | Poor |
| TOLLEFSON et al. (2001)[53] | WC | AA | NR | AA | AA | AA | AA | No | WC | PA | Poor |
| VOLAVKA et al. (2002)[58] | AA | PA | NAd | WC | PA | PA | AA | No | PA | NAd | Poor |
| VOLAVKA et al. (2004)[56] | AA | PA | NAd | WC | PA | PA | AA | No | PA | NAd | Poor |
| WEINER et al. (2010)[69] | AA | AA | PA | AA | AA | PA | AA | No | PA | NA | Poor |
| WIRSHING et al. (1999)[61] | WC | WC | NAd | NR | AA | PA | AA | Yes | AA | NAd | Poor |
| ZINK et al. (2009)[37] | AA | WC | NR | PA | WC | AA | AA | Yes | AA | NA | Poor |

# APPENDIX 15: DEFINITION OF SAE REPORTED IN INCLUDED RCTS

| Author | Definition of Serious/Severe Adverse Event |
|---|---|
| AKDEDE et al. (2005)[42] | NR |
| ANIL YAGCIOGLU et al. (2005)[45] | NR |
| ASSION et al. (2008)[49] | NR |
| AZORIN et al. (2001)[60] | NR |
| BONDOLFI et al. (1998)[66] | NR |
| CHANG et al. (2008)[38] | NR |
| CITROME et al. (2001)[59] | NR |
| CLAUS et al. (1992)[68] | NR |
| CONLEY et al. (1988)[65] | NR |
| CONLEY et al. (2003)[76] | NR |
| CZOBOR et al. (2002)[71] | NR |
| FLEISCHHACKER et al. (2010)[54] | Sinus tachycardia, severe psychotic disorder, severe hallucinations, “psychiatric disorders” |
| FREUDENREICH et al. (2007)[41] | NR |
| GENC et al. (2007)[50] | NR |
| GREEN at al. (1997)[67] | NR |
| HONER et al. (2006)[44] | No definition was provided. The patient reported to have SAE was described as his mental status having deteriorated over 1 to 2 weeks, required frequent restraint, had an elevated creatine kinase level (with no evidence of fever, rigidity, or autonomic instability). A history of neuroleptic malignant syndrome related to haloperidol. Treatment with the study medication was stopped, and the patient was admitted to a medical ward and subsequently recovered fully, from a medical perspective, and his mental status returned to the pre-study level of symptoms. The second patient with SAE was reported to have an exacerbation of auditory hallucination and suicidal ideation, requiring hospitalization. The third case had a self-inflicted scalp laceration that required stitches. |
| HONER et al. (2011)[72] | An AE occurring during any study phase, and at any dose, fulfilling one or more of the following criteria: resulted in death, was immediately life-threatening, require in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital abnormality or birth defect, was an important medical event that might have jeopardized the subject or might have required medical intervention to prevent one of the outcomes listed above. |

| Author | Definition of Serious/Severe Adverse Event |
|---|---|
| JOSIASSEN et al. (2005)[46] | NR |
| KANE et al. (2009)[36] | Agitation, psychotic disorder, suicidal ideation, and depression were reported as SAE. |
| KELLY et al. (2003)[48] | NR |
| KELLY et al. (2006)[43] | NR |
| KERN et al. (1998)[64] | NR |
| KERN et al. (1999)[62] | NR |
| KOTLER et al. (2004)[47] | NR |
| KUMRA et al. (2008)[40] | SAE definition was not provided. The 5 cases described as SAE were neutropenia, upper bowel obstruction, impaired glucose tolerance test (ITG), weight gain 7 pounds during the treatment by week 7 and drug-induced DM. |
| KUWILSKY et al. (2010)[55] | NR |
| LINDENMAYER et al. (2003)[57] | NR |
| McEVOY et al. (2006)[70] | NR |
| MELTZER et al. (2008)[39] | NR |
| MILLAR et al. (2008)[74] | NR |
| MOSSAHEB et al. (2006)[73] | NR |
| RICHARDSON et al. (2009)[75] | NR |
| ROSENHECK et al. (1999)[63] | NR |
| SHAFTI (2009)[52] | NR |
| SHILOH et al. (1997)[51] | NR |
| TOLLEFSON et al. (2001)[53] | NR |
| VOLAVKA et al. (2002)[58] | NR |
| VOLAVKA et al. (2004)[56] | NR |
| WEINER et al. (2010)[69] | NR |
| WIRSHING et al. (1999)[61] | NR |
| ZINK et al. (2009)[37] | NR |

# APPENDIX 16: COGNITION DATA

**Table A5: Cognition Data by MATRICS Consensus Cognitive Battery Domain for Clozapine-based Antipsychotic Combination Therapy versus Clozapine-Monotherapy Standard Dose**

| **Speed of Processing** | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Weiner 2010[69] 16 weeks | WAIS-III Digit Symbol Score | CLZ+RIS | 24 | Baseline mean: 49.3 (SD:14.06) Endpoint mean: 52.6 (SD: 16.40) | P=0.87 |
| | | CLZ+PLC | 28 | Baseline mean: 48.0 (SD: 14.1) Endpoint mean: 5.0 (SD:13.8) *There appears to be an error in the reported endpoint mean.* | |
| | Trails Making Test A (s) | CLZ+RIS | 24 | Baseline mean: 47.1 (SD: 28.14) Endpoint mean: 41.5 (SD: 18.0) | P=0.24 |
| | | CLZ+PLC | 28 | Baseline mean: 46.5 (SD: 14.8) Endpoint mean: 42.2 (SD: 13.1) | |
| | Trails Making Test B (s) | CLZ+RIS | 22 | Baseline mean: 130.0 (SD: 92.6) Endpoint mean: 117.1 (SD: 82.1) | P=0.91 |
| | | CLZ+PLC | 26 | Baseline mean: 46.5 (SD: 14.8) Endpoint mean: 42.2 (SD: 13.1) | |
| | Category Fluency Test (score) | CLZ+RIS | 24 | Baseline mean: 35.3 (SD: 9.8) Endpoint mean: 34.7 (SD: 8.6) | P=0.29 |
| | | CLZ+PLC | 28 | Baseline mean: 34.7 (SD: 9.4) Endpoint mean: 35.4 (SD: 11.0) | |
| | Controlled Oral Word Association (score) | CLZ+RIS | 24 | Baseline mean: 34.1 (SD: 12.6) Endpoint mean: 34.6 (SD: 12.4) | P=0.17 |
| | | CLZ+PLC | 28 | Baseline mean: 31.9 (SD: 12.5) Endpoint mean: 29.5 (SD: 12.6) | |

| | | | | | |
|---|---|---|---|---|---|
| Akdede 2006[42] 6 weeks | Controlled Word Association (sum of admissible words) | RIS+CLZ | 16 | Baseline mean: 31.1 (SE:1.36) Endpoint mean: 31.6 (SE: 1.45) | P=0.04 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 31.0 (SE: 1.45) Endpoint mean: 36.1 (SE: 1.45) | |
| | Stroop Test-colours (s) | RIS+CLZ | 16 | Baseline mean: 43.1 (SE:2.0) Endpoint mean: 46.6 (SE: 2.14) | P=0.03 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 45.8 (SE: 2.07) Endpoint mean: 39.6 (SE: 2.07) | |
| | Stroop Test-words (s) | RIS+CLZ | 16 | Baseline mean: 94.9 (SE: 2.81) Endpoint mean: 89.3 (SE: 3.03) | P=0.09 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 94.6 (SE: 3.02) Endpoint mean: 81.9 (SE: 3.02) | |
| | Stroop Test-interference (s) | RIS+CLZ | 16 | Baseline mean: 33.2 (SE: 0.85) Endpoint mean: 35.0 (SE: 0.92) | P=0.32 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 33.1 (SE: 0.88) Endpoint mean: 33.7 (SE: 0.88) | |
| **Attention/Vigilance** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Weiner 2010[69] 16 weeks | 2,3,4 Continuous Performance Test | CLZ+RIS | 18 | Baseline mean: 1.82 (SD: 0.61) Endpoint mean: 1.87 (SD: 0.68) | P=0.40 |
| | | CLZ+PLC | 19 | Baseline mean: 1.72 (SD: 0.75) Endpoint mean: 1.68 (SD: 0.74) | |
| **Working Memory (Non-Verbal)** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Weiner 2010[69] 16 weeks | Hershey Visuospatial Working Memory score | CLZ+RIS | 23 | Baseline mean: 28.2 (SD: 20.2) Endpoint mean: 24.5 (SD: 13.6) | P=0.24 |
| | | CLZ+PLC | 26 | Baseline mean: 38.8 (SD: 23.9) Endpoint mean: 33.3 (SD: 25.0) | |

| Working Memory (Verbal) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Akdede 2006[42] 6 weeks | Digit Span Test -total | RIS+CLZ | 16 | Baseline mean: 10.6 (SE:0.34) Endpoint mean: 11.0 (SE: 0.38) | P=0.20 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 10.7 (SE: 0.37) Endpoint mean: 11.7 (SE: 0.37) | |
| | Auditory Consonant Trigram Test | RIS+CLZ | 16 | Baseline mean: 38.0 (SE:0.85) Endpoint mean: 40.0 (SE: 0.90) | P=0.80 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 37.5 (SE: 0.90) Endpoint mean: 40.2 (SE: 0.90) | |
| Honer 2006[44] 8 weeks | Verbal working memory index derived from Letter-Number Sequencing and Brown-Peterson tests. | RIS+CLZ | 30 | Baseline mean: 0.09 (SD: 0.83) Endpoint mean: -0.08 (SD: 0.99) | P=0.02 |
| | | PLC+CLZ | 23 | Baseline mean: -0.10 (SD: 0.85) Endpoint mean: 0.14 (SD: 0.83) | |
| Weiner 2010[69] 16 weeks | WAIS-III Letter number sequencing score | CLZ+RIS | 24 | Baseline mean: 8.13 (SD: 2.80) Endpoint mean: 8.17 (SD: 2.84) | P=0.54 |
| | | CLZ+PLC | 28 | Baseline mean: 7.25 (SD: 2.58) Endpoint mean: 7.39 (SD: 2.39) | |

| Verbal Learning | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Weiner 2010[69] 16 weeks | Hopkins Verbal Learning Test Score (score) | CLZ+RIS | 24 | Baseline mean: 23.5 (SD: 7.9) Endpoint mean: 23.0 (SD: 8.0) | P=0.3 |
| | | CLZ+PLC | 28 | Baseline mean: 20.2 (SD: 5.7) Endpoint mean: 21.3 (SD: 6.0) | |
| Akdede 2006[42] 6 weeks | RAVLT-trial 1 (# words correctly recalled) | RIS+CLZ | 16 | Baseline mean: 4.9 (SE:0.32) Endpoint mean: 5.4 (SE: 0.32) | P=0.007 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 4.8 (SE: 0.22) Endpoint mean: 6.0 (SE: 0.23) | |
| | RAVLT-trials 1-5 (# words correctly recalled) | RIS+CLZ | 16 | Baseline mean: 36.6 (SE:1.12) Endpoint mean: 42.5 (SE: 1.20) | P=0.25 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 36.1 (SE: 1.20) Endpoint mean: 40.5 (SE: 1.2) | |
| | RAVLT-long-delay free recall (# words correctly recalled) | RIS+CLZ | 16 | Baseline mean: 6.9 (SE:0.42) Endpoint mean: 8.4 (SE: 0.45) | P=0.85 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 6.8(SE: 0.45) Endpoint mean: 8.3 (SE: 0.45) | |
| | RAVLT-recognition discriminability (# words correctly recalled) | RIS+CLZ | 16 | Baseline mean: 0.86 (SE:0.01) Endpoint mean: 0.84 (SE: 0.02) | P=0.07 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 0.85 (SE: 0.02) Endpoint mean: 0.89 (SE: 0.02) | |
| **Visual Learning** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Weiner 2010[69] 16 weeks | Brief Visuospatial Memory Test score (score) | CLZ+RIS | 24 | Baseline mean: 3.99 (SD: 2.14) Endpoint mean: 4.32 (SD: 2.17) | P=0.35 |
| | | CLZ+PLC | 28 | Baseline mean: 3.94 (SD: 1.85) Endpoint mean: 4.64 (SD: 2.11) | |

| Reasoning and Problem-Solving | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Weiner 2010[69] 16 weeks | WCST - categories completed | CLZ+RIS | 24 | Baseline mean: 1.29 (SD: 1.4) Endpoint mean: 1.67 (SD: 1.69) | P=0.88 |
| | | CLZ+PLC | 27 | Baseline mean: 1.33 (SD: 1.33) Endpoint mean: 1.59 (SD: 1.47) | |
| | WCST - % perseverative errors | CLZ+RIS | 24 | Baseline mean: 16.5 (SD: 10.8) Endpoint mean: 14.4 (SD: 10.9) | P=0.31 |
| | | CLZ+PLC | 27 | Baseline mean: 16.5 (SD: 9.4) Endpoint mean: 16.1 (SD: 9.5) | |
| **Social Cognition** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Other** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Akdede 2006[42] 6 weeks | Finger Tapping Test-dominant hand (mean # in 5s) | RIS+CLZ | 16 | Baseline mean: 41.7 (SE:1.2) Endpoint mean: 42.9 (SE: 1.3) | P=0.02 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 42.1 (SE: 1.3) Endpoint mean: 46.8 (SE: 1.3) | |
| | Finger Tapping Test - non-dominant hand (mean # in 5s) | RIS+CLZ | 16 | Baseline mean: 37.1 (SE:1.0) Endpoint mean: 39.2 (SE: 1.06) | P=0.04 (endpoint) |
| | | PLC+CLZ | 14 | Baseline mean: 36.8 (SE: 1.06) Endpoint mean: 43.1 (SE: 1.06) | |
| Weiner 2010[69] 16 weeks | Grooved Pegboard Score (mean of both hands) | CLZ+RIS | 23 | Baseline mean: 117.6 (SD: 39.3) Endpoint mean: 123.6 (SD: 49.0) | P=0.17 |
| | | CLZ+PLC | 28 | Baseline mean: 119.8 (SD: 42.8) Endpoint mean: 115.9 (SD: 35.6) | |

| Cognitive Symptom Scales or Interview-Based Assessments | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Fleischhacker 2010[54] 16 weeks | PANSS – cognitive subscale | CLZ+ARI | 46 | Difference of changes from baseline between groups: -0.3 (95% CI: -1.1, 0.4) | P=0.375 |
| | | CLZ+PLC | 48 | | |
| | GEOPTE - index | CLZ+ARI | 46 | Difference of changes from baseline between groups: -1.4 (95% CI: -4.4, 1.6) | P=0.348 |
| | | CLZ+PLC | 48 | | |

ARI = aripiprazole; BACS = Brief Assessment of Cognition in Schizophrenia; CLZ = clozapine; CVLT = California Verbal Learning Test; GEOPTE = Social Cognition in Schizophrenia/Psychosis Scale; (H) = high dose; Hal = haloperidol; OLZ = olanzapine; PANSS = Positive And Negative Symptoms Scale; PLC = placebo; QUET = quetiapine; (R) = standard dose; RAVLT = Rey Auditory Verbal Learning Test; RIS = risperidone; WAIS-III = Wechsler Adult Intelligence Scale – 3rd edition; WAIS-R = Wechsler Adult Intelligence Scale — revised (2nd) edition; WCST = Wisconsin Card Sorting Test; WISC-R = Wechsler Intelligence Scale for Children — Revised

**Table A6: Cognition Data by MATRICS Consensus Cognitive Battery Domain for Non-clozapine Antipsychotic Combination Therapy versus Non-clozapine Monotherapy**

| **Speed of Processing** | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Kane 2009[36] 16 weeks | Symbol coding score | (RIS or QUET) + ARI | 125 | Mean change from baseline 0.06 (SE: 0.64) | Non-significant |
| | | (RIS or QUET) + PLC | 116 | Mean change from baseline 0.03 (SE: 0.5) | |
| | Verbal Fluency Score | (RIS or QUET) + ARI | 124 | Mean change from baseline: -0.01 (SE: 0.70) | Non-significant |
| | | (RIS or QUET) + PLC | 117 | Mean change from baseline: 0.08 (SE: 0.67) | |
| **Attention/Vigilance** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Working Memory (Non-Verbal)** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Working Memory (Verbal)** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Kane 2009[36] 16 weeks | Verbal Memory Score | (RIS or QUET) + ARI | 126 | Mean change from baseline: 0.06 (SE: 1.01) | Non-significant |
| | | (RIS or QUET) + PLC | 118 | Mean change from baseline: -0.07 (SE: 0.92) | |
| | Digit Sequencing Score | (RIS or QUET) + ARI | 126 | Mean change from baseline: 0.02 (SE: 0.66) | Non-significant |
| | | (RIS or QUET) + PLC | 118 | Mean change from baseline: 0.1 (SE: 0.55) | |
| **Verbal Learning** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Visual Learning** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |

| Reasoning and Problem-Solving | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Kane 2009[36] 16 weeks | Tower of London (score) | (RIS or QUET) + ARI | 125 | Mean change from baseline: 0.39 (SE: 1.32) | Non-significant |
| | | (RIS or QUET) + PLC | 117 | Mean change from baseline: 0.19 (SE: 1.20) | |
| **Social Cognition** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Other** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Kane 2009[36] 16 weeks | BACS Composite Z-score | (RIS or QUET) + ARI | 125 | Mean change from baseline: 0.10 (SE: 0.63) | Non-significant |
| | | (RIS or QUET) + PLC | 117 | Mean change from baseline: 0.13 (SE: 0.61) | |
| | Token Motor Task Score | (RIS or QUET) + ARI | 124 | Mean change from baseline: 0.10 (SE: 0.04) | Non-significant |
| | | (RIS or QUET) + PLC | 115 | Mean change from baseline: 0.13 (SE: 1.16) | |
| **Cognitive Symptom Scales or Interview-Based Assessments** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |

ARI = aripiprazole; BACS = Brief Assessment of Cognition in Schizophrenia; CLZ = clozapine; CVLT = California Verbal Learning Test; GEOPTE = Social Cognition in Schizophrenia/Psychosis Scale; (H) = high dose; Hal = haloperidol; OLZ = olanzapine; PANSS = Positive and Negative Symptoms Scale; PLC = placebo; QUET = quetiapine; (R) = standard dose; RAVLT = Rey Auditory Verbal Learning Test; RIS = risperidone; WAIS-III = Wechsler Adult Intelligence Scale — 3rd edition; WAIS-R = Wechsler Adult Intelligence Scale — revised (2nd) edition; WCST = Wisconsin Card Sorting Test; WISC-R = Wechsler Intelligence Scale for Children — Revised.

**Table A7: Cognition data by MATRICS Consensus Cognitive Battery Domain for High-Dose Non-clozapine AAP Therapy versus Standard-Dose Clozapine**

| **Speed of Processing** | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Meltzer 2008[39] 6 months | WAIS-R Digit Symbol Substitution Test | OLZ (H) | 19 | Baseline mean: 34.6 (SE:1.4) Endpoint mean: 38.0 (SE: 1.5) | NR |
| | | CLZ (R) | 21 | Baseline mean: 34.5 (SE: 1.2) Endpoint mean: 42.4 (SE:1.7) | |
| | Controlled Word Association Test | OLZ(H) | 19 | Baseline mean: 25.3 (SE:1.2) Endpoint mean: 26.9 (SE: 1.4) | P=0.85 (endpoint) |
| | | CLZ (R) | 21 | Baseline mean: 25.3 (SE: 1.1) Endpoint mean: 27.3 (SE: 1.6) | |
| **Attention/Vigilance** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Working Memory (Non-Verbal)** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Working Memory (Verbal)** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Meltzer 2008[39] 6 months | Peterson Consonant Triagram Test | OLZ(H) | 19 | Baseline mean: 34.3 (SE:1.6) Endpoint mean: 33.7 (SE: 2.1) | NR |
| | | CLZ (R) | 21 | Baseline mean: 34.6 (SE: 1.5) Endpoint mean: 33.6 (SE: 2.2) | |

| Verbal Learning | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Meltzer 2008[39] 6 months | Verbal List Learning-Immediate Recall | OLZ(H) | 19 | Baseline mean: 29.2 (SE:1.6) Endpoint mean: 37.2 (SE: 2.0) | P=0.3 (endpoint) |
| | | CLZ (R) | 21 | Baseline mean: 29.9(SE: 1.4) Endpoint mean: 33.5 (SE: 2.8) | |
| | Verbal List Learning-Delayed Recall | OLZ(H) | 19 | Baseline mean: 5.5 (SE:0.5) Endpoint mean: 7.2 (SE: 0.7) | P=0.04 (endpoint) |
| | | CLZ (R) | 21 | Baseline mean: 5.8(SE: 0.5) Endpoint mean: 4.7 (SE: 0.9) | |
| **Visual Learning** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Reasoning and Problem- Solving** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| Meltzer 2008[39] 6 months | WISC-R Mazes (seconds?) | OLZ (H) | 19 | Baseline mean: 16.0 (SE:0.5) Endpoint mean: 18.5 (SE: 0.6) | P=0.002 (endpoint) |
| | | CLZ (R) | 21 | Baseline mean: 15.9 (SE: 0.5) Endpoint mean: 15.4 (SE: 0.7) | |
| | WCST-Categories Formed | OLZ (H) | 19 | Baseline mean: 3.0 (SE:0.2) Endpoint mean: 3.2 (SE: 0.3) | P=0.76 (endpoint) |
| | | CLZ (R) | 21 | Baseline mean: 3.0 (SE: 0.2) Endpoint mean: 3.1 (SE: 0.4) | |
| | WCST-% Perseveration | OLZ (H) | 19 | Baseline mean: 23.6 (SE:2.5) Endpoint mean: 24.8 (SE: 3.1) | P=0.92 (endpoint) |
| | | CLZ (R) | 21 | Baseline mean: 23.4 (SE: 2.5) Endpoint mean: 24.4 (SE: 3.7) | |

| Social Cognition | | | | | |
|---|---|---|---|---|---|
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Other** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |
| **Cognitive Symptom Scales or Interview-Based Assessments** | | | | | |
| **Study** | **Instrument** | **Treatment** | **No of Pts** | **Results** | **Reported Significance** |
| None found for this comparison | | | | | |

ARI = aripiprazole; BACS = Brief Assessment of Cognition in Schizophrenia; CLZ = clozapine; CVLT = California Verbal Learning Test; GEOPTE = Social Cognition in Schizophrenia/Psychosis Scale; (H) = high dose; Hal = haloperidol; OLZ = olanzapine; PANSS = Positive and Negative Symptoms Scale; PLC = placebo; QUET = quetiapine; (R) = standard dose; RAVLT = Rey Auditory Verbal Learning Test; RIS = risperidone; WAIS-III = Wechsler Adult Intelligence Scale — 3rd edition; WAIS-R = Wechsler Adult Intelligence Scale — revised (2nd) edition; WCST = Wisconsin Card Sorting Test; WISC-R = Wechsler Intelligence Scale for Children — Revised.

No cognition data were found for high-dose non-clozapine AAP versus standard-dose non-clozapine APD.

# APPENDIX 17: SUPPLEMENTAL SAFETY REVIEW

The randomized controlled trials (RCTs) included in CADTH's systematic review on combination and high-dose atypical antipsychotics for inadequately controlled patients with schizophrenia contained only limited data on the safety of these treatment strategies. To supplement this information, CADTH:

- Performed additional literature searches in the following bibliographic databases: MEDLINE (1950–) and MEDLINE In-Process & Other Non-Indexed Citations via Ovid. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Two separate searches were performed. The first search looked for review articles dealing with the safety of clozapine. The second looked for review articles dealing with the safety of any atypical antipsychotic, focusing on combination use or high doses. Retrieval was not limited by publication year, but was limited to the English or French language. The search was completed on July 7, 2010. Alerts were maintained until project completion.
- Obtained grey literature by searching the Advisories & Warnings section of CADTH's Grey Matters checklist.
- Reviewed safety information from reviews that presented safety data on combination antipsychotic treatment, high-dose atypical antipsychotic treatment, or clozapine at standard or high doses.
- Safety information from one continuation study of a large RCT included in the systematic review was also reviewed.

Safety information is presented in this review by outcome.

**Extrapyramidal Symptoms**

Limited supplemental evidence was identified pertaining to EPS outcomes for high-dose AAPs and no information was identified regarding EPS safety outcomes for combination treatment. All evidence identified was from narrative reviews[328-330] or expert opinion;[331] these studies provided information on clozapine,[328] asenapine,[329] risperidone,[328,330,331] quetiapine,[331] and aripiprazole.[331] Table A8 contains further detail regarding the included studies.

Based on the limited evidence available, patients with psychosis and tardive dyskinesia (TD) given higher doses of clozapine (up to 900 mg/day) showed improvements in TD over baseline[328] while patients with schizophrenia given risperidone 6 to 16 mg/day had lower TD scores compared with haloperidol.[328] Asenapine 20 mg/day did not seem to result in higher rates of EPS than placebo, but led to higher rates of akathisia, which was measured separately.[329] Review authors concluded that high doses of quetiapine (1,285.7 mg/d) likely have no effect on EPS symptoms during maintenance treatment.[331] Aripiprazole 45–90 mg/d for 45 days resulted in no clinically significant changes in "abnormal movement" compared with a standard dose.[331]

Although risperidone resulted in fewer EPS and required less frequent use of anticholinergic medication at standard doses compared with other AAPs, results were no longer significantly different at doses higher than 6 mg/day.[330] Additionally, 10 mg/day of risperidone resulted in worsened Parkinson's symptoms[331] compared with doses of 6 and 16 mg/day, and aripiprazole at doses of 90 mg/d resulted in higher rates of akathisia compared to other doses.[331]

| **Table A8:** Studies Reporting Extrapyramidal Outcomes | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **EPS Outcomes** |
| Tarsy et al. 2002[328] | Review; to review the extrapyramidal symptoms of AAPs; adult patients with schizophrenia or psychosis | Clozapine up to 900 mg/day, up to 36 months | 13 of 30 patients showed ≥ 50% improvement of TD compared with baseline |
| | | Risperidone 6–16 mg/d for 8 weeks | Lower TD scores than haloperidol |
| Citrome 2009[329] | Review; to review the efficacy and safety of asenapine for treatment of schizophrenia and bipolar disorder; patients with an acute exacerbation of schizophrenia, schizophrenia, schizoaffective disorder, or bipolar disorder | Asenapine 20 mg/d versus placebo | EPS rate (excluding akathisia): 12% NNH: 20 (95% CI NS)<br><br>Akathisia rate: 11% NNH: 13 (95% CI 8 to 30) |
| Haddad & Sharma 2007[330] | Review; to review the differential risks and clinical implications of AAP AEs; patients with schizophrenia or bipolar disorder | Risperidone at therapeutic doses versus risperidone 6 mg/d versus TAPs (mainly haloperidol) | At standard doses, RIS has less frequent EPS and requires less frequent usage of anticholinergics than TAPs. This difference disappeared when risperidone was > 6 mg/day |
| Goodnick 2005[331] | Review; expert opinion on higher than recommended doses of AAPs; patients with schizophrenia | Risperidone 10 mg/d | Worsened Parkinson's symptoms compared with placebo and both lesser (6 mg/d) and greater (16mg/d) doses. |
| | | Quetiapine 1,285.7 mg/d (average dose) | No effect on EPS parameters during an 11 week maintenance period |
| | | Aripiprazole 45, 60, 75, 90 mg/d for 45 days (control group 30 mg/d) | No clinically significant changes in measures of "abnormal movements" with increased dose. Higher incidence rate of akathisia with 90 mg/d dosing, but not at other doses. |

AAP = atypical antipsychotic; AE = adverse event; CI = confidence interval; EPS = extrapyramidal symptoms; mg/d = milligrams per day; NNH = number needed to harm; NS = not significant; RIS = risperidone; TAP = typical antipsychotic; TD = tardive dyskinesia; 95% CI = 95% confidence interval.

**Mortality Outcomes**

Limited evidence related to mortality was identified. Two narrative reviews[332,333] were identified reporting mortality for non-clozapine AAP combination therapy[332] and therapeutic doses of clozapine.[333] Table A9 contains further detail regarding the included studies.

The included literature reviews suggested reduced 10-year survival in patients prescribed more than one antipsychotic medication[332] compared with those given only one, based on a prospective cohort study. An epidemiological study found a higher mortality ratio, rate of sudden death, and rate of "disease related death" for patients treated with therapeutic doses of clozapine versus the general population.[333] This should be considered in light of a higher mortality ratio for all patients with schizophrenia compared with the general population, largely due to risk of suicide; however, the most common causes of death in the clozapine users were external factors and circulatory diseases, while suicides were reduced.[333]

**Table A9:** Studies Reporting Mortality Outcomes

| Author, Year | Study Type; Study Objective; Study Population | AAP Treatment | Safety Outcomes |
|---|---|---|---|
| Freudenreich & Goff 2002[332] | To review the literature regarding efficacy and risks of combination therapy (AAPs or conventional); patients with schizophrenia | More than one antipsychotic | Reduced survival in a study cohort within a 10-year prospective study (relative risk 2.46)<br><br>(no further details reported) |
| Trenton et al. 2003[333] | To review fatalities associated with therapeutic use and overdose of AAPs; patients with schizophrenia (for clozapine-treated patients: those who have not responded to other treatment options) | Therapeutic doses of clozapine (normal therapeutic dose range defined as 300–600 mg/day with a maximum of 900 mg/day) | 396 deaths per 85,399 patient years (compared with 229 in regular population).<br><br>Mortality ratio for CLZ-treated patients compared with general pop: 1.73 (95% CI, 1.56 to 1.91).<br><br>Sudden death in CLZ patients 3.8 times higher than psychiatric patients not taking CLZ and the rate of "disease related death" was 5 times higher. |

AAP= atypical antipsychotic; AE = adverse event; avg = average; CLZ = clozapine; mg/d = milligrams per day.

**Hyperprolactinemia**

Three reviews[331,332,334] and one RCT continuation trial[294] examining combination treatment,[294,332,334] clozapine treatment,[294] high-dose quetiapine treatment,[331] and high-dose aripiprazole treatment[331] and reporting prolactin outcomes were identified. Table A10 contains further detail regarding the included studies.

In these reviews, clozapine therapy in combination with other antipsychotic agents resulted in increased serum prolactin levels compared with clozapine monotherapy[332,334] or clozapine combined with placebo.[334] High-dose quetiapine (average 1,286 mg/d) resulted in a minor reduction in prolactin levels compared with baseline in one open-label study, while in another, no serum prolactin changes at a maximum dose of 1,600 mg/day were found.[331] High-dose aripiprazole did not affect serum prolactin in a pharmacokinetic study in patients with stable schizophrenia or schizoaffective disorder.[331]

Clozapine at therapeutic doses and combination AAP treatment (specific combinations not reported) resulted in decreased prolactin levels compared with baseline in the CATIE III continuation trial, though the results were not statistically significant.[294]

**Table A10:** Studies Reporting Prolactin Outcomes

| Author, Year | Study Type; Study Objective; Study population | AAP Treatment | Prolactin Outcomes |
|---|---|---|---|
| Stroup et al. 2009 CATIE III[294] | RCT; continuation trial to compare the effectiveness of AAP treatment; 270 patients with schizophrenia. | Combination AAP treatment 40 patients (mostly those who had stopped previous treatment due to inefficacy) | Prolactin (ng/mL): Mean: -1.6 SD: 20.7 Median: -2.0 Adjusted mean (n=31): -1.9 SE: 3.3 |
| | | Clozapine at therapeutic doses, 37 patients (mostly those who had stopped previous treatment due to inefficacy) | Prolactin (ng/mL): Mean: -9.8 SD: 15.0 Median: -2.9 Adjusted mean (n=31): -8.2, SE: 3.3 |
| Freudenreich & Goff 2002[332] | Review; to review the literature regarding efficacy and risks of combination therapy (AAPs or conventional); patients with schizophrenia | Clozapine + Risperidone vs. Clozapine alone | Prolactin levels: Combination: 35.76 ng/mL CLZ: 8.42 ng/mL |
| Chong & Remington 2000[334] | Review; to review the safety and efficacy of clozapine augmentation; patients with schizophrenia, schizoaffective disorder, and bipolar disorder | Clozapine (400 mg/d) + sulpiride (400 mg/d) | 4- to 7-fold increase in serum prolactin levels compared with CLZ alone or CLZ plus placebo |
| Goodnick 2005[331] | Review; expert opinion on higher than recommended doses of AAPs; patients with schizophrenia | Quetiapine 1,285.7 mg/d | Prolactin level reduction of 11.65 ng/mL |
| | | Quetiapine max 1,600/day | No significant changes |
| | | Aripiprazole 45, 60, 75, 90 mg/d for 45 days (control group 30 mg/d) | No changes in prolactin levels |

AAP = atypical antipsychotic; AE = adverse event; CLZ = clozapine; mg/d = milligrams per day; ng/mL = nanograms per millilitre; SD = standard deviation; SE = standard error.

**Glucose intolerance or insulin resistance**

Limited evidence was identified regarding the effect of high-dose or combination AAP treatment on glucose levels: one review[331] and one RCT continuation trial.[294] The review did not find a statistically significant change in blood glucose with doses of quetiapine 1,600 mg/day compared with baseline levels after open label treatment.[331] In the CATIE III trial, clozapine treatment tended to increase blood glucose levels and combination AAP treatment tended to result in decreased blood glucose levels (results not statistically significant).[294] Table A11 contains further details regarding the included studies.

**Table A11:** Studies Reporting Blood Glucose Outcomes

| Author, Year | Study Type; Study Objective; Study Population | AAP Treatment | Glucose Outcomes |
|---|---|---|---|
| Stroup et al. 2009 CATIE III[294] | RCT; continuation trial to compare the effectiveness of AAP treatment; 270 patients with schizophrenia. | Combination AAP treatment 40 patients (mostly those who had stopped previous treatment due to inefficacy) | Blood glucose (mg/dL): Mean: -2.3 SD: 30.5 Median: 0.5 Exposure adjusted: (n=31) Mean: -7.6 SE: 6.8 |
| | | Clozapine at therapeutic doses, 37 patients (mostly those who had stopped previous treatment due to inefficacy) | Blood glucose (mg/dL): Mean: 9.0 SD: 34.0 Median: 10.0 Exposure adjusted: (n=32) Mean: 10.0 SE: 6.6 |
| Goodnick, 2005[331] | Review, Expert opinion on higher than recommended doses of AAPs; patients with schizophrenia | Quetiapine max 1,600 mg/day | No significant changes |

AAP = atypical antipsychotic; mg/d = milligrams per day; mg/dL = milligrams per decilitre; SD = standard deviation SE = standard error.

**Weight Gain**

One systematic review,[335] two narrative reviews,[330,335] and one RCT continuation trial[294] were identified reporting on the effect of clozapine,[330] high-dose[294,331,335] or combination AAP[294] treatment on weight gain. Table A12 contains further detail regarding the included studies.

Combination[294] and clozapine treatment[294,330,335] were associated with increases in body weight of more than 7%[294] and more than 10%,[330] with standard doses being associated with higher weight gain than high-dose treatment in the included systematic review.[335]

Treatment with high-dose risperidone injection[335] and doses of up to 1,600 mg/d of quetiapine[331] were not associated with increased weight gain over standard doses. In a small retrospective, uncontrolled study, quetiapine doses up to 2,000 mg were associated with significant weight gain.[257] Olanzapine treatment at doses higher than 20 mg/day was associated with a significant effect on weight gain (patients taking more than 20 mg/day gained more weight than those taking lower doses), but these changes were less than 7% and were not considered clinically significant by the authors.[335]

| **Table A12:** Studies Reporting Weight Gain Outcomes | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Weight Gain Outcomes** |
| Stroup et al. 2009 CATIE III[294] | RCT; continuation trial to compare the effectiveness of AAP treatment; 270 patients with schizophrenia. | Combination AAP treatment 40 patients (mostly those who had stopped previous treatment due to inefficacy) | Number of patients with weight gain >7%: 12/31 (39%)<br>mean weight change in lbs: 8.4 SD 14.8<br>median: 11<br>range (from 5th to 95th percentile): -16, 29 |
| | | Clozapine at therapeutic doses, 37 patients (mostly those who had stopped previous treatment due to inefficacy) | Number of patients with weight gain >7%: 10/31 (32%)<br>mean weight change in lbs: 8.8, SD 24.2<br>median: 3<br>range (from 5th to 95th percentile): -19, 53 |
| Simon et al. 2009[335] | Systematic review; explore relationship between dosage of AAPs and metabolic side effects; mostly patients with schizophrenia | Clozapine 220 mg/d vs. 608 mg/d | Weight gain occurred in both groups but was higher (mean 12.5kg) in low dose responders than in high dose responders (mean 5kg); low dose responders had 5kg lower weight at baseline. |
| | | Risperidone injection, 25 mg, 50 mg, 75 mg | no correlation between dose of RIS and weight gain<br>25mg: 1.5kg<br>50mg: 2.6 kg<br>75 mg: 1.9 kg |
| | | Olanzapine 10 mg, 20 mg, 40 mg | Significant dose-related change in mean weight gain between 10 mg and 40 mg groups (though not the 20 mg group) but no correlation between weight gain and OLZ plasma concentration. Weight gain was not considered clinically significant >= 7% |
| | | Olanzapine 20 mg–40 mg | OLZ doses over 20 mg/d were associated with significant weight gain compared to lower doses (F=3.9, df= 1.42; P<0.05) |
| | | Olanzapine 30 mg for 10 d and 40 mg for 10d | 27% of patients gained weight |

| **Table A12:** Studies Reporting Weight Gain Outcomes | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Weight Gain Outcomes** |
| | | Olanzapine 40 mg for 20 d | 14% of patients gained weight |
| Haddad & Sharma 2007[330] | Review; to review the differential risks and clinical implications of AAP AEs; patients with schizophrenia or bipolar disorder | Clozapine at therapeutic doses | First year: 58%-70% gain >10% body weight, weight gain consistent through first 4 years, levels at 5 years |
| Goodnick 2005[331] | Review; expert opinion on higher than recommended doses of AAPs; patients with schizophrenia | Olanzapine > 50 mg/d | Average weight gain: 7.5 lbs (small study, 13 people, crossover) |
| | | Quetiapine max 2000 mg/day 4–24 months | 3 of 7 patients with significant weight gain (39–70 lbs) |
| | | Quetiapine max 1600 mg/day | No significant weight gain |

AAP = atypical antipsychotic; d = day; kg = kilogram; lbs = pounds; m = milligrams; mg/d = milligrams per day; OLZ = olanzapine; RIS = risperidone; SD = standard deviation.

**Hospitalizations**

Only one citation reporting hospitalizations was identified.[294] The CATIE III continuation trial found that the risk of hospitalization was highest for patients using combination AAP treatment compared to therapeutic doses of clozapine, as well as standard doses of other atypical antipsychoics.[294] Table A13 contains further detail regarding the included study.

| **Table A13:** Details Regarding Hospitalization | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Hospitalization Outcomes** |
| Stroup et al. 2009 CATIE III[294] | RCT; continuation trial to compare the effectiveness of AAP treatment; 270 patients with schizophrenia. | Combination AAP treatment 40 patients (mostly those who had stopped previous treatment due to inefficacy) | Hospitalizations due to exacerbation of schizophrenia: 10 (25%)<br><br>Number of hospitalizations/person years of exposure: 14/28<br>Risk ratio: 0.49 |
| | | Clozapine at therapeutic doses, 37 patients (mostly those who had stopped previous treatment due to inefficacy) | Hospitalizations due to exacerbation of schizophrenia:<br>10 (16%)<br><br>Number of hospitalizations/person years of exposure: 6/20<br>Risk ratio: 0.30 |

AAP = atypical antipsychotic; RCT = randomized controlled trial.

**Myocarditis**

Three identified reviews examined myocarditis associated with both standard[91,330,333] and high-dose clozapine treatment.[333] Myocarditis risk seemed to be highest within the first few weeks[333] to two months[330] of clozapine treatment. Although uncommon (incidence estimated between 0.7% and 1.2%), the review authors concluded that myocarditis is an important adverse event associated with clozapine therapy and warrants further study.[91] Table A14 contains further detail regarding the included studies.

**Table A14:** Studies Reporting Myocarditis

| Author, Year | Study Type; Study Objective; Study Population | AAP Treatment | Safety Outcomes |
|---|---|---|---|
| Haas et al. 2007[91] | Review; retrospectively review all adverse drug reaction reports voluntarily submitted to Australian adverse drug reactions unit mentioning suspected myocarditis associated with clozapine; patients with schizophrenia | Clozapine 100–450 mg/d | 105 cases* (estimate of number of patients taking CLZ: 10,031–17,075) |
| | | Clozapine at any dose | 116 cases,* 12 (10.3%) with fatal outcomes, 10 were confirmed cardiac deaths.<br><br>1993–2003 incidence between 0.7% and 1.2%<br><br>All cases:<br>Median time to onset: 17 days<br>Mean time to onset: 171.7 days (SD 530.9)<br>Range: 1–3,285 days<br>Mode: 15 days<br><br>Most cases (93 cases of myocarditis within 6 months of start of therapy)<br>Median time to onset: 16 days<br>Mean: 19.8 days (SD 17.3)<br>Range: 1–120<br>Mode: 15 |
| Trenton et al. 2003[333] | Review; to review fatalities associated with therapeutic use and overdose of AAPs; patients with schizophrenia (for clozapine-treated patients: those who have not responded to other treatment options) | Clozapine at therapeutic doses (normal therapeutic dose range defined as 300–600 mg/day with a maximum of 900 mg/day) | 8 patients between 1983 and 1999 in Sweden, 3 deaths |
| | | Clozapine 100–725 mg/day | 8,000 pts on clozapine, 15 cases of myocarditis, 8 of cardiomyopathy. Of those 23, 5 with myocarditis, 1 with |

| **Table A14:** Studies Reporting Myocarditis | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Safety Outcomes** |
| | | | cardiomyopathy died, all deaths within 14-18 days of starting clozapine treatment. |
| Haddad & Sharma 2007[330] | Review; to review the differential risks and clinical implications of AAP AEs; patients with schizophrenia or bipolar disorder | Clozapine at therapeutic doses | Estimates of myocarditis vary from 1 in 500 to 1 in 10,000. Risk of myocarditis highest in 1st 2 months |

AAP = atypical antipsychotic; AE = adverse event; CLZ = clozapine; mg/d = milligrams per day; pts = patients; SD = standard deviation.
* Reviewed records between 1990 and 2003, most reports were 2000–2003 (82 of the reports — 70.7%) 116 reported patients, 90 male, 22 female (4 unspecified)
Minimum no. pts exposed to CLZ: 10,031
Maximum no. exposed: 17,075

### Pancreatitis

Pancreatitis may be associated with AAP combination treatment.[336] Based on a pharmacovigilance study of pooled spontaneous adverse events, clozapine combination therapy (either with another AAP or with haloperidol) was associated with more instances of pancreatitis than olanzapine combination therapy and risperidone therapy.[336] Significance was not tested and while the estimated number of prescriptions for clozapine, olanzapine, and risperidone monotherapy was reported, estimated number of patients receiving combination treatment was not reported. There was a temporal relationship found between the start of drug therapy and the onset of pancreatitis; pancreatitis was most likely to occur within the first six months of treatment. Table A15 contains further detail regarding the included study.

| **Table A15:** Details Regarding Pancreatitis Outcomes | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Pancreatitis Outcomes** |
| Koller et al. 2003[336] | Pharmacovigilance study of pooled spontaneously reported adverse events; investigate the relative numbers, clinical characteristics of pancreatitis associated with AAPs vs. haloperidol using MEDWATCH reports | Clozapine combination therapy (either with another AAP or with haloperidol) | 10 cases, mean age 36.2 SD 16.7, male/female ratio 4:1 |
| | | Olanzapine combination therapy (with another AAP or haloperidol) | 7 cases, mean age 38.0 SD 12.5, male/female ratio: 6:1 |
| | | Risperidone combination therapy (with another AAP or haloperidol) | 2 cases, mean age 46.0 SD 35.4, male/female ratio: 0:2 |

AAP = atypical antipsychotic; AE = adverse event; mg/d = milligrams per day; SD = standard deviation.

**Other Adverse Events**

Other adverse events reported include agranulocytosis,[333] incidence of diabetes,[333] seizures,[330] and completed suicides.[329] Table A16 contains further detail regarding the included studies.

High-dose clozapine treatment was associated with higher seizure rates than lower doses of clozapine and other antipsychotics administered at standard doses.[330] Rates of clozapine-associated agranulocytosis (at standard doses) were reported as having decreased since the advent of the Clozapine National Registry.[333] Standard doses of clozapine were also found to be associated with new-onset diabetes.[333] Completed suicides were found to be more common in patients treated with high-dose asenapine than with olanzapine at standard doses.[329]

**Table A16:** Details of Other Adverse Events

| Author, Year | Study Type; Study Objective; Study Population | AAP Treatment | Adverse Event | Outcome |
|---|---|---|---|---|
| Trenton et al. 2003[333] | Review; to review fatalities associated with therapeutic use and overdose of AAPs; patients with schizophrenia (for clozapine-treated patients: those who have not responded to other treatment options) | Clozapine at therapeutic doses (normal therapeutic dose range defined as 300–600 mg/day with a maximum of 900 mg/day) | Agranulocytosis | 17 cases in 3,000 according to 1977 Finnish research<br><br>Clozapine National Registry data 1990–1994:<br>99,502 patients on CLZ, 382 cases agranulocytosis — rate of 0.38% (pre-CNR rate was 1%–2%) |
| | | Clozapine at therapeutic doses (normal therapeutic dose range defined as 300–600 mg/day with a maximum of 900 mg/day) | Incidence of diabetes | USDA medwatch showed 131 new-onset diabetes cases, and 11 exacerbations associated with clozapine. 37 of those were likely diabetic ketoacidosis, 8 deaths |
| Haddad & Sharma 2007[330] | Review; to review the differential risks and clinical implications of AAP AEs; patients with schizophrenia or bipolar disorder | Clozapine > 600 mg/day | Seizure rate | Seizure rate 4.4% at > 600 mg/day versus 1% at < 300 mg/day |
| Citrome 2009[329] | Review; to review the | Asenapine 10–20 mg/day | Completed suicides | 0.6%<br>(vs. 0.3% in standard |

| Table A16: Details of Other Adverse Events | | | | |
|---|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Adverse Event** | **Outcome** |
| | efficacy and safety of asenapine for treatment of schizophrenia and bipolar disorder; patients with an acute exacerbation of schizophrenia, schizophrenia, schizoaffective disorder, or bipolar disorder | | | dose OLZ-treated patients) |

AAP = atypical antipsychotic; AE = adverse event; CLZ = clozapine; CNR = clozapine national registry; mg/d = milligrams per day; OLZ = olanzapine.

**Any Adverse Event**

Limited information was available regarding any serious adverse event associated with combination or high-dose AAP treatment. In the continuation of the CATIE trial (Phase 3), clozapine therapy at standard doses was associated with a slightly higher incidence of serious adverse events than combination therapy (results not statistically significant).[294] While the reported serious adverse events occurred in less than 20% of patients taking combination AAP treatment or clozapine, 65% of combination AAP-treated patients and 78% of clozapine-treated patients experienced a moderate to severe adverse event.[294] A narrative review reported that high-dose asenapine was associated with an overall serious adverse event rate of 16% compared with olanzapine (12%), risperidone (18%), haloperidol (11%), and placebo (10%) at standard doses.[329] A second review found no difference in rates of adverse events between two high-dose ziprasidone treatment regimens.[331] Table A17 contains further detail regarding the included studies.

| Table A17: Studies Reporting Adverse Event Rates | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Safety Outcomes** |
| Stroup et al. 2009 CATIE III[294] | RCT; continuation trial to compare the effectiveness of AAP treatment; 270 patients with schizophrenia. | Combination AAP treatment 40 patients (mostly those who had stopped previous treatment due to inefficacy) | Any serious AE: 6 (15%)<br><br>Any moderate to severe AE: 26 (65%) |
| | | Clozapine at therapeutic doses, 37 patients (mostly those who had stopped | Any serious AE: 7 (19%)<br><br>Any moderate to |

| **Table A17:** Studies Reporting Adverse Event Rates | | | |
|---|---|---|---|
| **Author, Year** | **Study Type; Study Objective; Study Population** | **AAP Treatment** | **Safety Outcomes** |
| | | previous treatment due to inefficacy) | severe AE: 29 (78%) |
| Citrome 2009[329] | Review; to review the efficacy and safety of asenapine for tx of schizophrenia and bipolar disorder; patients with an acute exacerbation of schizophrenia, schizophrenia, schizoaffective disorder, or bipolar disorder | Asenapine 10–20 mg per day (versus standard doses of olanzapine, risperidone, haloperidol, placebo) | 16% serious adverse event rate<br><br>(olanzapine: 12%, risperidone: 18%, haloperidol: 11%, placebo: 10%) |
| Goodnick 2005[331] | Review; expert opinion on higher than recommended doses of AAPs; patients with schizophrenia | Ziprasidone ≥ 240 mg/d, ≥ 320 mg/day | No differences in AE rates between the two doses. |

AAP = atypical antipsychotic; AE = adverse event; mg/d = milligrams per day; SAE = serious adverse event.

**Summary**

For the most part, high-dose AAPs do not seem to increase EPS, though there are reports of increased akathisia. Higher mortality has been reported with either combination or clozapine therapy. High-dose and AAP therapy do not appear to have negative effects on prolactin levels, though CLZ combination therapy may increase prolactin compared with CLZ monotherapy. While CLZ therapy has been associated with diabetes,[333] statistically significant differences in glucose levels or diabetes were not specifically reported. High-dose and combination therapy have been reported to statistically significantly affect body weight, though these differences may not always be clinically significant. Combination AAP use may be associated with an increased risk of hospitalization compared with standard-dose CLZ or other AAPs. Both standard and high-dose CLZ appear to be associated with myocarditis, while the association between CLZ combination therapy and pancreatitis is less clear. High-dose CLZ may increase the risk of seizures compared with standard dose, while high-dose asenapine may increase the risk of suicide compared with standard-dose olanzapine. Very limited data were found regarding overall incidence of adverse events.

Overall, the safety evidence for high-dose and combination AAP therapy, as well as clozapine therapy, is limited and often contradictory. Because most of the identified studies were observational, results may be confounded by various sources of bias. The possibility of indication bias is of particular concern in comparisons of clozapine, combination therapy, or high-dose therapy with standard-dose non-clozapine antipsychotic monotherapy, since the former are more likely to be used in patients with refractory or severe disease. Such patients may have a higher risk of adverse effects or mortality independent of therapy.

# APPENDIX 18: SUMMARY OF INCLUDED STUDIES NOT INCLUDED IN THE REFERENCE CASE META-ANALYSES

| Study | Intervention/Comparator Doses | Reason Excluded from Ref Case | Comparison with Ref Case |
|---|---|---|---|
| MILLAR et al. (2008)[74] | ARI+CLZ: 4 to 15 mg/d ARI, CLZ dose not reported<br>PLC+CLZ: CLZ dose not reported | Abstract | The effect size was not significantly altered from the reference case analysis. |
| MOSSAHEB et al. (2006)[73] | Hal+CLZ<br>4 mg/d Hal and 450±70.7 mg/d CLZ<br>PLC+CLZ<br>500±81.7 mg/d CLZ | Abstract | |
| RICHARDSON et al. (2009)[75] | RIS+CLZ: 4 mg/d RIS; CLZ dose not reported<br>PLC+CLZ: CLZ dose not reported | Abstract | |
| KUMRA et al. (2008)[40] | OLZ (H): 26.2 ± 6.5 mg/d<br>CLZ: 403.1 ± 201.8 mg/d | Adolescent population | |
| JOSIASSEN et al. (2005)[46] | RIS+CLZ (H)<br>4.43±1.5 mg/d RIS and ≥ 600 mg/d CLZ (H)<br>PLC+CLZ (H)<br>≥ 600 mg/d CLZ | Mixed treatment strategies (comb. and high dose) | Sensitivity analysis by adding these data to meta-analysis for (CLZ comb vs. CLZ mono) was done. The effect size was not significantly altered from reference case analysis. |
| KOTLER et al. (2004)[47] | Sulpiride+OLZ(H):<br>up to 600 mg/d Sul and 22.4±4.37 mg/d OLZ<br>OLZ(H):<br>22.4±4.37 mg/d OLZ (no placebo) | Mixed treatment strategies (comb and high dose) | Sensitivity analysis by adding these data to meta-analysis for (non CLZ comb vs. Non-CLZ mono) was done. The effect size was not significantly altered from reference case analysis. |
| SHAFTI (2009)[52] | Fluphenazine+OLZ(H)<br>17.42±6.07 mg/2 wks FLU and 21.96±5.03 mg/d OLZ<br>PLC+OLZ(H): 21.96±5.03 mg/d OLZ | Mixed treatment strategies (comb and high dose) | |
| GENC et al. (2007)[50] | AMI+CLZ<br>437±104 mg/d AMI and 536–550 mg/d CLZ<br>QUET+CLZ<br>596 mg/d QUET and 536–550 mg/d CLZ | Comb vs. Comb. | Since the intervention strategies used in the two RCTs were different, data could not be pooled. In terms of PANSS score, WDAE and all-cause WD, CGI-S, no statistically significant differences between AMI+CLZ and QUET+CLZ or between RIS+CLZ and ZIP+CLZ were found in patients inadequately controlled on CLZ monotherapy . |
| ZINK et al. (2009)[37] | RIS+CLZ<br>3.82 ± 1.8 mg/d RIS and 437.5±140.4 mg/d CLZ<br>ZIP+CLZ<br>134±34.4 mg/d ZIP and 370.8±150.0 mg/d CLZ | Comb vs. Comb. | |

| Study | Intervention/Comparator Doses | Reason Excluded from Ref Case | Comparison with Ref Case |
|---|---|---|---|
| KUWILSKY et al. (2010)[55] | See ZINK et al. (2009)[37] | Duplicate data/ multiple reporting. | Duplicate data were not reported. |
| CITROME et al. (2001)[59] | See Volavka 2002[58] | Duplicate/ multiple reporting. | Duplicate data were not reported. |
| Czobor et al. (2002)[71] | See Volavka 2002[58] | Duplicate/ multiple reporting. | |
| VOLAVKA et al. 2004[56] | See Volavka 2002[58] | Duplicate/ multiple reporting. | |
| GREEN et al. (1997)[67] | See WIRSHING et al. (1999)[61] | Duplicate/ multiple reporting. | |
| KERN et al. (1998)[64] | See WIRSHING et al. (1999)[61] | Duplicate/ multiple reporting. | |
| KERN et al. (1999)[62] | See WIRSHING et al. (1999)[61] | Duplicate/ multiple reporting. | |
| AKDEDE et al. (2005)[42] | See Anil et al. (2005)[45] | Duplicate/ multiple reporting. | |
| KELLY et al. (2006)[43] | CONLEY et al. (2003)[76] | Duplicate/ multiple reporting. | |
| CONLEY et al. (2003)[76] | OLZ (H): 50 mg/d<br>CLZ: 450 mg/d | Duplicate/ multiple reporting. | Duplicate data were not reported. |
| CONLEY et al. (1988)[65] | OLZ (H)+PLC: 25 mg/d<br>Chlor+Benz: 1,200 mg/d chlorpromazine and 4 mg/d benztropine mesylate | AAP (H) vs. TAP (H) (CPZ >1,000 mg/ d) | When these data were added, the effect size was not significantly altered from reference case analysis. |
| WIRSHING et al. (1999)[61] | RIS (H): 7.5 ± 1.9 mg/d<br>Hal: 19.4 ± 5.6 mg/d | AAP (H) vs. TAP (H) (Halo >10 mg/d) | |
| ROSENHECK et al. (1999)[63] | CLZ(H): 628 mg/d<br>Hal: 28.2 mg/d | AAP (H) vs. TAP (H) (Halo >10 mg/d) | |