Journal:
Pediatric Drugs

Title:
Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis

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APPENDICES

Appendix A (Search strategy)

The Cochrane library

#1 MeSH descriptor: [Safety] explode all trees
#2 Safet* (Word variations have been searched)
#3 Side effect* (Word variations have been searched)
#4 Undesirable effect* (Word variations have been searched)
#5 Toxicit* (Word variations have been searched)
#6 Adverse drug reaction* (Word variations have been searched)
#7 Adverse drug effect* (Word variations have been searched)
#8 Adverse drug outcome* (Word variations have been searched)
#9 Adverse drug event* (Word variations have been searched)
#10 Tolerab* (Word variations have been searched)
#11 MeSH descriptor: [Mortality] explode all trees
#12 Mortalit* (Word variations have been searched)
#13 Death (Word variations have been searched)
#14 fatal (Word variations have been searched)
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 MeSH descriptor: [Antipsychotic Agents] explode all trees
#17 Antipsychotic* (Word variations have been searched)
#18 Antipsychotic Agent* (Word variations have been searched)
#19 Antipsychotic Drug* (Word variations have been searched)
#20 Antipsychotic Effect* (Word variations have been searched)
#21 Typical antipsychotic* (Word variations have been searched)
#22 Atypical antipsychotic* (Word variations have been searched)
#23 first generation antipsychotic* (Word variations have been searched)
#24 Second generation antipsychotic* (Word variations have been searched)
#25 levomepromazin* (Word variations have been searched)
#26 chlorpromazin* (Word variations have been searched)
#27 methotrimeprazin* (Word variations have been searched)
#28 promazin* (Word variations have been searched)
#29 Pericyazin* (Word variations have been searched)
#30 thioridazin* (Word variations have been searched)
#31 pipotiazin* (Word variations have been searched)
#32 fluphenazin* (Word variations have been searched)
#33 perphenazin* (Word variations have been searched)
#34 prochlorperazin* (Word variations have been searched)
#35 trifluoperazin* (Word variations have been searched)
#36 benperidol* (Word variations have been searched)
#37 droperidol* (Word variations have been searched)
#38 haloperidol* (Word variations have been searched)
#39 flupentixol* (Word variations have been searched)
#40 thiothixen* (Word variations have been searched)
#41 zuclopenthixol* (Word variations have been searched)
#42 pimozid* (Word variations have been searched)
#43 sulpirid* (Word variations have been searched)

#44 loxapin* (Word variations have been searched)
#45 oxypertin* (Word variations have been searched)
#46 amisulprid* (Word variations have been searched)
#47 clozapin* (Word variations have been searched)
#48 olanzapin* (Word variations have been searched)
#49 paliperidon* (Word variations have been searched)
#50 quetiapin* (Word variations have been searched)
#51 lurasidon* (Word variations have been searched)
#52 asenapin* (Word variations have been searched)
#53 iloperidon* (Word variations have been searched)
#54 risperidon* (Word variations have been searched)
#55 aripiprazol* (Word variations have been searched)
#56 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or 53 or #54 or #55
#57 MeSH descriptor: [Child Development Disorders, Pervasive] explode all trees
#58 Autis* (Word variations have been searched)
#59 Autism spectrum disorder* (Word variations have been searched)
#60 ASD* (Word variations have been searched)
#61 Infantile autism
#62 Early infantile autism
#63 Kanner* (Word variations have been searched)
#64 Rett* (Word variations have been searched)
#65 Asperger* (Word variations have been searched)
#66 Pervasive* development* disorder* (Word variations have been searched)
#67 PDD* (Word variations have been searched)
#68 #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or#66 or #67
#69 #15 and #56 and #68

PsychINFO

1. exp PATIENT SAFETY/ or exp SAFETY/
2. (Safet* or Side effect* or Undesirable effect* or Toxicit* or Adverse drug reaction* or Adverse drug outcome* or Adverse drug effect* or Adverse drug event* or Drug* toxicit* or Drug* safet* or Patient* safet* or Adverse effect* or Adverse reaction* or Adverse event* or Drug side effect* or (Drug-related side effect* and adverse reaction*) or Long term adverse effect*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3. exp "Side Effects (Drug)"/
4. (Drug tolerabil* or Tolerabil*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
5. exp "Death and Dying"/
6. (Mortalit* or Death or Fatal).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Haloperidol/ or exp Risperidone/ or exp Neuroleptic Drugs/ or exp Olanzapine/ or exp Clozapine/
9. (Antipsychotic* or Antipsychotic agent* or Antipsychotic drug* or Antipsychotic agent*, butyrophenone or Antipsychotic agent*, phenothiazine or Antipsychotic agent*, thioxanthene or Antipsychotic agent*, diphenylbutylpiperidine or Antipsychotic agent*, Substituted benzamide or Antipsychotic agent*, dibenzoxazepine or Neuroleptic* or Neuroleptic drug* or Major tranquilizer* or Tranquilizing agent*, major or Classical antipsychotic* or Typical neuroleptic* or Typical antipsychotic* drug* or Atypical antipsychotic* drug* or First generation antipsychotic* or Second generation antipsychotic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
10. (Chloropromazin* or levomepromazin* or methotrimeprazin* or promazin* or pericyazin* or thioridazin* or pipotiazin* or fluphenazin* or perphenazin* or prochlorperazin* or trifluoperazin* or benperidol* or droperidol* or haloperidol*or flupentixol* or thiothixen* or zuclopenthixol* or pimozid* or sulpirid* or loxapin* or oxypertin* or amisulprid* or clozapin* or olanzapin* or paliperidon* or quetiapin* or lurasidon* or asenapin* or iloperidon* or risperidon* or aripiprazol*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
11. 8 or 9 or 10
12. exp Autism Spectrum Disorders/
13. (((Autis* spectrum disorder or Autis* or ASD or ASDs or Autistic child* or Autistic disorder or Infantile autism or Early infantile autism or Childhood autism or Classical autism or Typical autism or Kanner syndrome or Kanner* or Asperger* or Rett* or Child development disorders, pervasive or Pervasive) adj3 child*) or Pervasive development* disorder* or PDD or PDDs).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
14. 12 or 13
15. 7 and 11 and 14

Embase

1. exp drug safety/ or exp patient safety/ or exp safety/
2. (Safet* or Side effect* or Undesirable effect* or Toxicit* or Adverse drug reaction* or Adverse drug outcome* or Adverse drug effect* or Adverse drug event* or Drug toxicit* or Drug* safet* or Patient* safet* or Adverse effect* or Adverse reaction* or Adverse event* or Drug side effect* or (Drug-related side effect* and adverse reaction*) or Long term adverse effect*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
3. exp drug tolerability/
4. (Drug Tolerabil* or Tolerab*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. exp mortality/
6. (Mortalit* or Death or Fatal).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp neuroleptic agent/
9. (Antipsychotic* or Antipsychotic agent* or Antipsychotic drug* or Antipsychotic agent*, butyrophenone or Antipsychotic agent*, phenothiazine or Antipsychotic agent*, thioxanthene or Antipsychotic agent*, diphenylbutylpiperidine or Antipsychotic agent*, Substituted benzamide or Antipsychotic agent*, dibenzoxazepine or Neuroleptic* or Neuroleptic drug* or Major tranquilizer* or Tranquilizing agent*, major or Classical antipsychotic* or Typical neuroleptic* or Typical antipsychotic* drug* or Atypical antipsychotic* drug* or First generation antipsychotic* or Second generation antipsychotic*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
10. (Chloropromazin* or levomepromazin* or methotrimeprazin* or promazin* or pericyazin* or thioridazin* or pipotiazin* or fluphenazin* or perphenazin* or prochlorperazin* or trifluoperazin* or benperidol*or droperidol* or haloperidol* or flupentixol* or thiothixen* or zuclopenthixol* or pimozid* or sulpirid* or loxapin* or oxypertin* or amisulprid* clozapin* or olanzapin* or paliperidon* or quetiapin* or lurasidon* or asenapin* or iloperidon* or risperidon* or aripiprazol*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
11. 8 or 9 or 10
12. exp autism/
13. (((Autis* spectrum disorder or Autis* or ASD or ASDs or Autistic child* or Autistic disorder or Infantile autism or Early infantile autism or Childhood autism or Classical autism or Typical autism or Kanner syndrome or Kanner* or Asperger* or Rett* or Child development disorders, pervasive or Pervasive) adj3 child*) or Pervasive development* disorder* or PDD or PDDs).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
14. 12 or 13
15. 7 and 11 and 14

Medline

1. exp Patient Safety/ or exp Safety/
2. (Safet* or Side effect* or Undesirable effect* or Toxicit* or Adverse drug reaction* or Adverse drug outcome* or Adverse drug effect* or Adverse drug event* or Drug toxicit* or Drug* safet* or Patient* safet* or Adverse effect* or Adverse reaction* or Adverse event* or Drug side effect* or (Drug-related side effect* and adverse reaction*) or Long term adverse effect*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. (Drug tolerabil* or Tolerabil*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. exp Mortality/
5. (Mortalit* or Death or Fatal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. 1 or 2 or 3 or 4 or 5
7. exp Antipsychotic Agents/
8. (Antipsychotic* or Antipsychotic agent* or Antipsychotic drug* or Antipsychotic agent*, butyrophenone or Antipsychotic agent*, phenothiazine or Antipsychotic agent*, thioxanthene or Antipsychotic agent*, diphenylbutylpiperidine or Antipsychotic agent*, Substituted benzamide or Antipsychotic agent*, dibenzoxazepine or Neuroleptic* or Neuroleptic drug* or Major tranquilizer* or Tranquilizing agent*, major or Classical antipsychotic* or Typical antipsychotic* drug* or Atypical antipsychotic* drug* or First generation antipsychotic* or Second generation antipsychotic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. (Chloropromazin* or levomepromazin* or methotrimeprazin* or promazin* or pericyazin* or thioridazin* or pipotiazin* or fluphenazin* or perphenazin* or prochlorperazin* or trifluoperazin* or benperidol*or droperidol* or haloperidol* or flupentixol* or thiothixen* or zuclopenthixol* or pimozid* or sulpirid* or loxapin* or oxypertin* or amisulprid* clozapin* or olanzapin* or paliperidon* or quetiapin* or lurasidon* or asenapin* or iloperidon* or risperidon* or aripiprazol*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. 7 or 8 or 9
11. exp Asperger Syndrome/ or exp Autistic Disorder/ or exp Autism Spectrum Disorder/
12. (((Autis* spectrum disorder or Autis* or ASD or ASDs or Autistic child* or Autistic disorder or Infantile autism or Early infantile autism or Childhood autism or Classical autism or Typical autism or Kanner syndrome or Kanner* or Asperger* or Rett* or Child development disorders, pervasive or Pervasive) adj3 child*) or Pervasive development* disorder* or PDD or PDDs).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. 11 or 12
14. 6 and 10 and 13

Appendix B (Quality assessment)

1- Assessment of RCTs using Cochrane Collaboration tool.

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel***	**Blinding of outcome assessment***	**Incomplete outcome data***	**Selective reporting**
McCracken et al. (2005)[1]	**Judgment**	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk
	Support	'Eligible subjects were randomly assigned to receive risperidone or placebo for 8 weeks; details are provided elsewhere (4)'	(description of allocation is not included)	(open label phase)	'assessed by a blinded clinician'	(the dropout and reasons were reported)	(reported AE as stated in method)
Anderson GM et al. (2007)[2]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(did not report the no. of lost F/U)	(reported AE as stated in method)
McCracken Jt et al. (2002)[3]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	'it was assessed by two clinicians who were unaware of the treatment assignment'	(the withdrawal and reasons were reported)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Vo Lc et al. (2016)[4]	Judgment	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(the electrophysiologist was blinded)	(clarify the completeness of outcome data and analysis)	(reported AE as stated in method)
Findling RL et al. (2014)[5]	Judgment	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(reported the reason for discontinuation in each arm)	(reported AE as stated in method)
Gencer O et al. (2008)[6]	Judgment	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(open label phase)	(Assessment blinding were not specified)	(clarified the completeness of outcome data and analysis)	(reported AE as stated in method)
Ghanizadeh A et al. (2014)[7]	Judgment	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(participants were blinded)	(the clinicians was blinded)	(clarified the completeness of outcome data and analysis)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel***	**Blinding of outcome assessment***	**Incomplete outcome data***	**Selective reporting**
Ichikawa H et al. (2017)[8]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(The investigators and subjects were blinded to the trial drug randomisation code)	(The investigators and subjects were blinded to the trial drug randomisation code)	(clarified the completeness of outcome data)	(reported AE as stated in method)
Ichikawa H et al. (2017)[9]	**Judgment**	High risk	High risk	High risk	Unclear risk	Low risk	Low risk
	Support	(no randomisation, it is one arm study)	(no allocation concealment)	(open label phase)	(Assessment blinding were not specified)	(reported the reason for discontinuation)	(reported AE as stated in method)
Nikvarz N et al. (2017)[10]	**Judgment**	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk
	Support	'Patients were randomly allocated to receive treatments based on simple, balanced, blocked randomization'	(description of allocation is not included)	(open label phase)	(Assessment blinding were not specified)	(clarified the completeness of outcome data)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel***	**Blinding of outcome assessment***	**Incomplete outcome data***	**Selective reporting**
Loebel, A et al. (2016)[11]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	'randomized, double-blind, in a 1:1:1 ratio (via an interactive voice/web response system)'	randomized, double-blind, in a 1:1:1 ratio (via an interactive voice/web response system)	(double blind)	(The investigators and subjects were blinded to the trial drug randomisation code)	(clarified the completeness of outcome data)	(reported AE as stated in method)
Kent, Jm et al. (2013)[12]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	'The randomization was conducted by using randomly permuted blocks'	used randomized blocks of subjects for allocation	(double blind)	(The investigators and subjects were blinded to the trial drug randomisation code)	(clarified the completeness of outcome data)	(reported AE as stated in method)
Kent, Jm et al. (2013)[13]	**Judgment**	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk
	Support	(randomisation, continued from RCT phase)	(description of allocation is not included)	(open label phase)	(Single blind (both site and staff) not for participants and evaluator)	(clarify the completeness of outcome data)	(reported AE as stated in method)
Stigler, Ka et al. (2012)[14]	**Judgment**	High risk	High risk	High risk	Unclear risk	Low risk	Low risk
	Support	(non- randomised)	(no allocation concealment)	(open label phase)	(Assessment blinding were not specified)	(described dropout)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel***	**Blinding of outcome assessment***	**Incomplete outcome data***	**Selective reporting**
Marcus, RN et al. (2009)[15]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(clarify the completeness of outcome data)	(reported AE as stated in method)
Owen, R et al. (2009)[16]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	'a computer-generated randomization schedule using a permuted block design'	'Investigational sites accessed a call-in interactive voice response system when patients were ready to be randomly assigned. The system assigned a medication bottle number to each patient.'	(double blind, participants and investigator)	(double blind, participants and investigator)	(reported the reason for discontinuation)	(reported AE as stated in method)
Marcus, Rn et al. (2011)[17]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(reported the reason for discontinuation)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Hellings, JA et al. (2010)[18]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described the reason of withdrawal)	(reported AE as stated in method)
Stigler, KA et al. (2009)[19]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described the reason of withdrawal)	(reported AE as stated in method)
Capone, GT et al. (2008)[20]	**Judgment**	High risk	High risk	High risk	High risk	High risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(did not report the no. of lost F/U or give any reasons)	(reported AE as stated in method)
Troost, PW et al. (2007)[21]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described the reason of withdrawal)	(reported AE as stated in method)
Pandina, Gj et al. (2007)[22]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(described the reason of withdrawal or incompleteness of data)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel***	**Blinding of outcome assessment***	**Incomplete outcome data***	**Selective reporting**
Malone, RP et al. (2007)[23]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(clarify the response rate and performed LOCF for analysis)	(reported AE as stated in method)
Nagaraj, R et al. (2006)[24]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	(generated a randomization sequence)	(used randomized blocks of subjects for allocation)	(double blind)	(persons engaged in interviewing and administering the test instruments were blinded)	(described the reason of withdrawal or incompleteness of data)	(reported AE as stated in method)
Luby, J et al. (2006)[25]	**Judgment**	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk
	Support	'Randomization table obtained from the WUSM pharmacy and derived using a standard software package.'	(description of allocation is not included)	(double blind)	(psychiatrists were not blinded to the treatment condition)	(all participants completed the trial)	(reported AE as stated in method)
Hollander, E et al. (2006)[26]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(described the drop out and gave reasons)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Troost, Pieter W. (2005)[27]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)
Shea, S (2004)[28]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(described the drop out and gave reasons and use ITT as an analysis)	(reported AE as stated in method)
Gagliano, A. (2004)[29]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(outcome assessment was un-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Malone, Richard P. (2002)[30]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(outcome assessment was un-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Kemner, C. (2002)[31]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(outcome assessment was un-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Masi, G. (2001)[32]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)
Masi, Gabriele (2001)[33]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)
Masi, Gabriele (2001)[34]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Nicolson, Rob (1998)[35]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)
McDougle, Christopher J. (1997)[36]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Findling, R. L. (1997)[37]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel***	**Blinding of outcome assessment***	**Incomplete outcome data***	**Selective reporting**
Remington, G (2001)[38]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(reported the incompleteness of data) (reported the incompleteness of data)	(reported AE as stated in method)
Scahill, L (2016)[39]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(clinicians and evaluators were blinded)	(reported the incompleteness of data and showed the differences between included subjects and dropped out subjects)	(reported AE as stated in method)
McDougle, Christopher J. (1998)[40]	**Judgment**	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	'patients were randomly allocated according to a computer-generated list'	(description of allocation is not included)	(double blind)	(clinicians and evaluators were blinded)	(reported the incompleteness of data)	(reported AE as stated in method)

Appendix B (Quality assessment)

2- Assessment of observational studies using an adapted version of modified Newcastle-Ottawa scale (NOS).

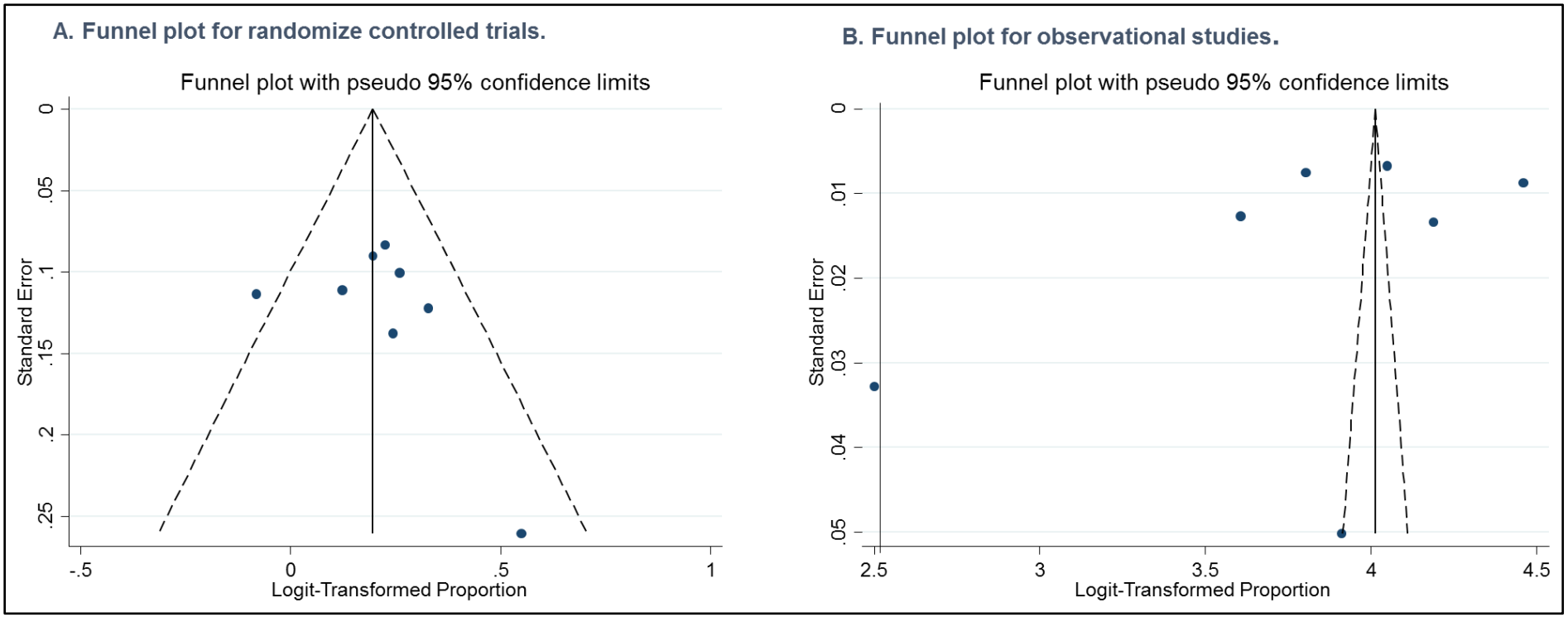
0-3 (0 definitely no, 3 definitely yes)

Domain of evaluation		Masi G, et al. (2003)[41]	Corson A H, et al. (2004)[42]	Masi G, et al. (2009)[43]	Beherec L, et al. (2011)[44]	Boon-Y V, et al. (2014)[45]	Wink L K, et al. (2014)[46]	Aman M, et al. (2015)[47]
Methods for selecting study participants (i.e. Selection bias)	Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?	2	2	2	1	2	2	3
Methods to control confounding (i.e. Performance bias)	Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?	1	1	1	0	1	2	2
	Did the study identify and adjust for any variables or confounders that may influence the outcome?	2	1	2	1	2	1	2
Statistical methods (i.e. Detection bias)	Did the study use appropriate statistical analysis methods relative to the outcome of interest?	3	2	3	2	3	2	3
	Is there little missing data and did the study handle it accordingly?	2	2	2	2	2	2	2
Methods for measuring outcome variables (i.e. Information bias)	Is the methodology of the outcome measurement explicitly stated and is it appropriate?	2	2	3	2	1	2	3
	Is there an objective assessment of the outcome of interest?	2	2	3	1	2	2	2

Domain of evaluation		Hellings J A, et al. (2015)[48]	Hongkaew Y, et al. (2015)[49]	Ngamsamut N, et al. (2016)[50]	Nuntamool N, et al. (2017)[51]	Srisawasdi P, et al. (2017)[52]	Vanwong N, et al (2017)[53]	Wink L K, et al. (2017)[54]
Methods for selecting study participants (i.e. Selection bias)	Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?	2	2	2	2	2	2	3
Methods to control confounding (i.e. Performance bias)	Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?	2	2	2	2	2	2	2
	Did the study identify and adjust for any variables or confounders that may influence the outcome?	2	2	1	2	3	1	2
Statistical methods (i.e. Detection bias)	Did the study use appropriate statistical analysis methods relative to the outcome of interest?	3	3	3	3	3	2	3
	Is there little missing data and did the study handle it accordingly?	2	2	2	2	2	2	2
Methods for measuring outcome variables (i.e. Information bias)	Is the methodology of the outcome measurement explicitly stated and is it appropriate?	3	3	3	3	3	2	3
	Is there an objective assessment of the outcome of interest?	2	2	2	3	2	2	2

Appendix C (Publication bias)

Figure 5: Publication bias funnel plots.



Tests for RCTs' Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = 6
Std. Dev. of Score = 8.08
Number of Studies = 8
z = 0.74
Pr > |z| = 0.458
z = 0.62 (continuity corrected)
Pr > |z| = 0.536 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0557482	.1869998	0.30	0.776	-.4018237	.5133201
bias	1.316251	1.690496	0.78	0.466	-2.820243	5.452745

Tests for Observational Studies' Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = -5
Std. Dev. of Score = 6.66
Number of Studies = 7
z = -0.75
Pr > |z| = 0.453
z = 0.60 (continuity corrected)
Pr > |z| = 0.548 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	4.240709	.2841422	14.92	0.000	3.510299	4.97112
bias	-24.74086	27.41186	-0.90	0.408	-95.20528	45.72356

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