



Clinical effectiveness analysis of naltrexone versus acamprosate and placebo in alcohol dependent patients treated with psychotherapy

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Background

Alcohol dependence is a complex of physiological, behavioural and cognitive phenomena, in which the acquisition and consumption of alcohol has a much higher priority for a given individual than other behaviours, which once had a greater impact¹. Alcohol dependence is characterised by craving, tolerance, a preoccupation with alcohol and continued drinking in spite of harmful consequences (for example, liver disease or depression caused by drinking).

Adepen® (naltrexone hydrochloride) is used as an additional therapy to support abstinence and to reduce the craving for alcohol within a comprehensive treatment programme (psychotherapy) for alcohol dependence². Alcohol has an euphoric effect, and the more often it is abused, the more its lack is felt as an unpleasant sensation that can be removed by another drinking session and putting oneself in euphoric state. The euphoric effect of alcohol is the result of, among other things, stimulation of endorphin secretion, which stimulate opioid receptors³. Naltrexone hydrochloride competitively binds to receptors located in the central and peripheral nervous system, blocking access to exogenously administered opioids².

Objective

Assessment of the clinical effectiveness of naltrexone versus acamprosate and placebo in alcohol dependent patients receiving psychotherapy.

Methods

Analysis was conducted in accordance with the principles of systematic review, based on the Cochrane Collaboration guidelines and the guidelines of the Polish Agency for Health Technology Assessment. A systematic search of Medline, EmBase, Cochrane and CRD database and clinical trials registry was performed in order to find relevant publications using the terms: naltrexone and alcoholism and their synonyms (until June 2010). Studies selected for inclusion were based on a pre-defined protocol with the following PICOS scheme:

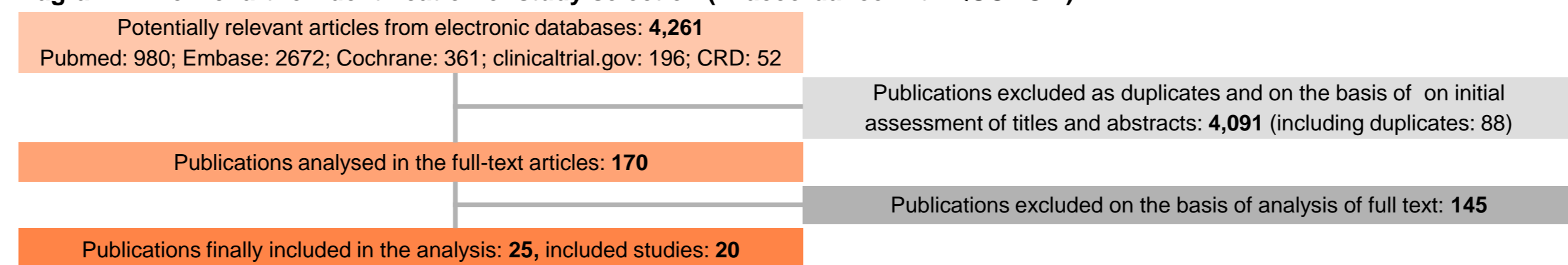
Population:	adults who are dependent on alcohol and treated with psychotherapy;
Intervention:	naltrexone administered in combination with psychotherapy;
Control groups:	1) acamprosate administered in combination with psychotherapy, 2) placebo in combination with psychotherapy;
Outcomes:	total abstinence (percentage of patients remaining abstinent), duration of abstinence, relapse (time to first and subsequent relapses; percentages of patients who have relapsed), adherence/compliance, measurement of liver biomarkers (GGT, AST, ALT), subjective evaluation of the feeling of craving, quality of life, withdrawal from the study (in total, due to adverse events, due to lack of efficacy), death, adverse events;
Study type:	head-to-head RCT trials conducted in parallel groups; single-blind, double-blind trials; treatment duration ≥ 12 weeks.

All decisions regarding the inclusion/exclusion criteria of studies involved at least two independent reviewers, with discrepancies resolved by a third reviewer. The reference lists of identified articles were then examined for additional publications. Calculations were performed using the StatsDirect® 2.6.8 statistical package.

Results

Out of 4,261 publications screened, 170 publications were analysed in full-text version, of which 25 publications (20 studies) met the criteria for inclusion (Diagram 1). All studies included into analysis were double-blind, randomised clinical trials (subtype II A). Among them, 3 studies (Kiefer 2003^{15,16}, Morley 2006²⁰, Rubio 2001^{2a}) directly compare clinical effectiveness of naltrexone combined with psychotherapy (NAL/PSY) versus acamprosate combined with psychotherapy (ACA/PSY). Direct comparison of clinical efficacy and safety of naltrexone combined with psychotherapy versus placebo combined with psychotherapy (PL/PSY) was evaluated in 19 studies (Ahmadi 2002⁴, Ahmadi 2004⁵, Anton 1999^{6,7}, Anton 2005⁸, Baltieri 2008¹⁰, Baldin 2003⁹, Chick 2000¹¹, Gaspar 2002¹², Guardia 2002¹³, Huang 2005¹⁴, Kiefer 2003, Krystal 2001^{17,18}, Latt 2002¹⁹, Morley 2006²⁰, Morris 2001²¹, O'Malley 1992^{22,23}, O'Malley 2008²⁴, Volpicelli 1992^{26,27}, Volpicelli 1997²⁸).

Diagram 1. Flow chart for identification of study selection (in accordance with QUOROM)



Clinical effectiveness analysis of naltrexone versus acamprosate in alcohol dependent patient receiving psychotherapy in short (12 weeks) and long (12 months) observation period.

Table 1. Summary results (efficacy) NAL/PSY vs. ACA/PSY

Intervention	Endpoint	Study	OR (95% CI)	NNT/NNH
Short observation period: 12 weeks				
NAL/PSY vs. ACA/PSY	Absolute abstinence	Morley 2006	1.22 (0.41; 3.69)	-
	Compliance	Morley 2006	2.58 (0.65; 12.34)	-
	Relapse	Kiefer 2003, Morley 2006	0.76 (0.41; 1.41)	-
Difference in final means MD (95% CI)				
NAL/PSY vs. ACA/PSY	Accumulated abstinence	Morley 2006	-8.5 (-18.77; 1.77)	-
	Times to first relapse	Morley 2006	5.6 (-7.03; 18.23)	-
	Time to first lapse	Morley 2006	0.2 (-11.99; 12.39)	-
	Symptom Checklist 90	Kiefer 2003	5.0 (-11.35; 21.35)	-
	GGT level	Kiefer 2003	9.7 (5.18; 14.22)	-
Long observation period: 12 months				
NAL/PSY vs. ACA/PSY	Abstinence	Rubio 2001	3.00 (1.47; 6.17)	4 (3; 10)
	Relapse	Rubio 2001	0.30 (0.13; 0.66)	5 (3; 11)
NAL/PSY vs. ACA/PSY	Adjunctive treatment			
	Disulfiram	Rubio 2001	0.26 (0.12; 0.54)	4 (3; 7)
	Sertraline	Rubio 2001	1.04 (0.06; 16.77)*	-
NAL/PSY vs. ACA/PSY	Difference in final means MD (95% CI)			
	Accumulate abstinence	Rubio 2001	63 (24.72; 101.28)	-
	Times to first relapse	Rubio 2001	21 (10.03; 31.97)	-
NAL/PSY vs. ACA/PSY	Time to first alcohol consumption	Rubio 2001	5.0 (-5.07; 15.07)	-
	Duration of adherence to treatment	Rubio 2001	9.00 (7.12; 10.88)	-
	GGT levels	Rubio 2001	3.0 (-6.0; 12.0)	-
SMD (95% CI)				
NAL/PSY vs. ACA/PSY	Number of drinks consumed at one time	Rubio 2001	-0.77 (-1.09; -0.44)	-
	Composite craving severity score	Rubio 2001	-0.36 (-0.67; -0.04)	-

Statistically significant results are bolded. *Calculated using the Peto method. SMD-standardised mean difference; MD-mean difference; NNT-number needed to treat; NNH-number needed to harm; OR-odds ratio; CI-confidence interval, vs.-versus; GGT-gamma-glutamyl transpeptidase.

Conclusions

- Adepen® (naltrexone hydrochloride) administered orally plus psychotherapy for alcohol-dependent patients results in a higher clinical effectiveness and comparable safety profile in comparison with acamprosate administered with psychotherapy for a 1-year-long observation treatment.
- Naltrexone together with psychotherapy brings higher clinical efficacy and a comparable safety profile compared to placebo, both in the short (12-16 weeks) and medium (24 weeks and 36 weeks) observation period. Long-term results (52 weeks) of the analysis quoted indicate comparable clinical efficacy (no statistical significance of the results obtained) of the use of naltrexone and placebo in the group of alcohol-dependent patients undergoing psychotherapy.
- Adverse drug reactions related to the use of naltrexone were usually mild and transient. The most frequent ones included: headaches, sleeping disorders, fatigue, anxiety, and gastro-intestinal disorders such as abdominal pain, nausea, and vomiting.
- The results of the analysis carried univocally prove that naltrexone administered at a dose of 50 mg a day is an effective and safe drug in the treatment of alcohol dependent patients who additionally undergo psychotherapy.

Clinical effectiveness analysis of naltrexone versus placebo in alcohol dependent patient receiving psychotherapy in short (12 – 16 weeks), medium (24 weeks and 36 weeks) and long (52 weeks) observation period.

Table 2. Summary results (efficacy) – NAL/PSY vs. PL/PSY

Intervention	Endpoint	Study	OR (95% CI)	NNT
Short observation period: 12 weeks				
NAL/PSY vs. PL/PSY	Absolute abstinence	Anton 1999, Baltieri 2008, Chick 2000, Gaspar 2002, Morley 2006, Morris 2001, O'Malley 1992, O'Malley 2008, Volpicelli 1995	1.46 (1.10; 1.93)	13 (8; 50)
	Compliance ≥ 70%	Anton 1999, Chick 2000, Morley 2006, Morris 2001, Volpicelli 1997	1.44 (0.96; 2.17)	-
	Relapse	Anton 1999, Anton 2005, Gaspar 2002, Guardia 2002, Kiefer 2003, Krystal 2001, Latt 2002, Morley 2006, Morris 2001, O'Malley 1992, O'Malley 2008, Volpicelli 1995, Volpicelli 1997	0.48 (0.36; 0.64)	7 (5; 11)
WMD (95% CI)				
NAL/PSY vs. PL/PSY	Percentage of days abstinence	Anton 1999, Anton 2005, Guardia 2002, Morris 2001, O'Malley 2008	8.72 (7.38; 10.06)	-
	Accumulated abstinence (days)	Morley 2006	1.10 (-10.09; 12.29)	-
	Accumulated abstinence (weeks)	Baltieri 2008	1.00 (-0.87; 2.87)	-
	Time to first lapse (days)	Anton 1999, Guardia 2002, Morley 2006	1.83 (-3.18; 6.53)	-
	Times to first relapse (days)	Anton 1999, Krystal 2001, Morley 2006	9.86 (4.77; 14.56)	-
	Times to first relapse (weeks)	Baltieri 2008	0.70 (-1.14; 2.54)	-
	Percentage of medication compliance	Anton 1999, Anton 2005, Guardia 2002, Krystal 2001, Morris 2001	1.02 (-0.87; 2.91)	-
	Percentage of heavy drinking days	O'Malley 2008	-7.5 (-8.91; -6.09)	-
	Percentage of heavy drinking weeks	Baltieri 2008	-0.90 (-2.81; 1.01)	-
	Percentage of drinking days	Krystal 2001, O'Malley 1992, Volpicelli 1995, Volpicelli 1997	-4.30 (-4.16; -2.44)	-
Difference in mean changes MD (95% CI)				
NAL/PSY vs. PL/PSY	GGT levels	Anton 1999, Anton 2005, Baltieri 2008, Latt 2002, Morris 2001, Volpicelli 1995, Volpicelli 1997	-9.26 (-18.46; -0.06)	-
	AST levels	Latt 2002, O'Malley 1992, Volpicelli 1995, Volpicelli 1997	-7.89 (-18.79; 3.00)	-
	ALT levels	Latt 2002, Morris 2001	0.07 (-6.00; 6.13)	-
	GGT level change from baseline	Kiefer 2003, O'Malley 2008	6.88 (-15.00; 29.75)	-
	Mean number of drinks consumed per drinking day	Anton 1999, Anton 2005, Guardia 2002, Krystal 2001, Morley 2006, Morris 2001, O'Malley 2008	-0.28 (-0.50; -0.07)	-

Statistically significant results are bolded; SMD-standardised mean difference; MD-mean difference; WMD-weighted mean difference; NNT-number needed to treat; OR-odds ratio; CI-confidence interval, vs.-versus; GGT-gamma-glutamyl transpeptidase, ALT-alanine transaminase, AST-asparagine transferase.

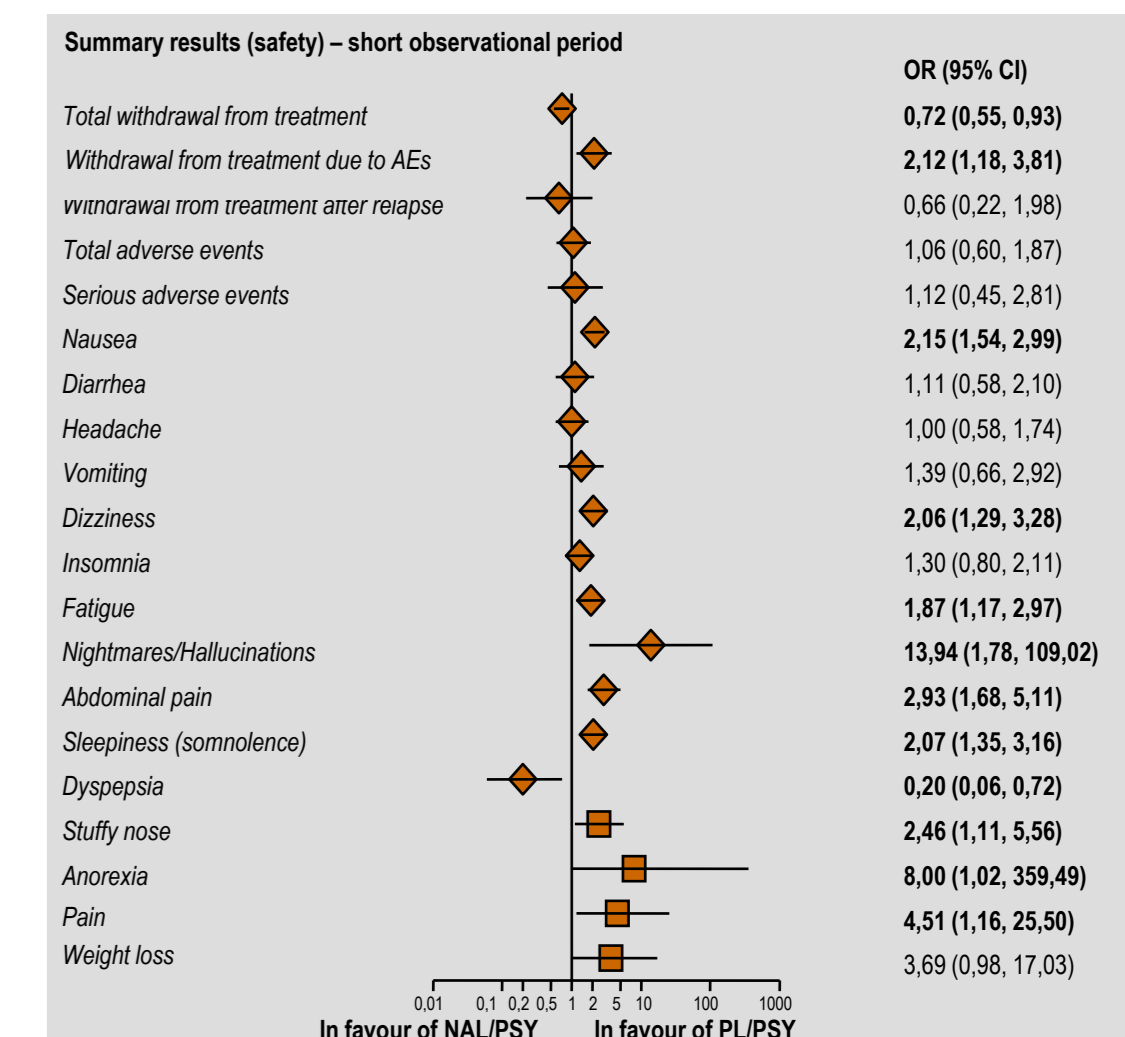
Table 3. Summary results (efficacy) – medium (24; 36 weeks) and long (52 weeks) observational period

Intervention	Endpoint	Study	OR (95% CI)	NNT/NNH
Medium observation period: 24 weeks				
NAL/PSY vs. PL/PSY	Relapse	Baldin 2008	1.22 (0.20; 8.69)	-
	Compliance ≥ 80%	Baldin 2008	0.70 (0.22; 2.11)	-
Difference in final means MD (95% CI)				
NAL/PSY vs. PL/PSY	Time to first relapse	Baldin 2008	18.50 (16.53; 20.47)	-
	Percentage of HDD	Baldin 2008	-11.00 (-18.18; -3.82)	-
	Percentage of drinking days	Baldin 2008	-10.50 (-18.10; -2.90)	-
	Assessment of depression symptoms in the SCL-90 scale	Baldin 2008	-0.03 (-0.15; 0.09)	-
	ALT level	Baldin 2008	-0.65 (-0.94; -0.36)	-
SMD (95% CI)				
NAL/PSY vs. PL/PSY	AST level	Baldin 2008	-0.14 (-0.19; -0.10)	-
	ALT level	Baldin 2008	-0.14 (-0.22; -0.06)	-
Long observation period: 52 weeks				
NAL/PSY vs. PL/PSY	Relapse	Ahmadi 2004	0.43 (0.18; 1.00)	6 (3; 37)
	Remission (no relapse)	Ahmadi 2004	2.33 (0.99; 5.55)	6 (3; 67)

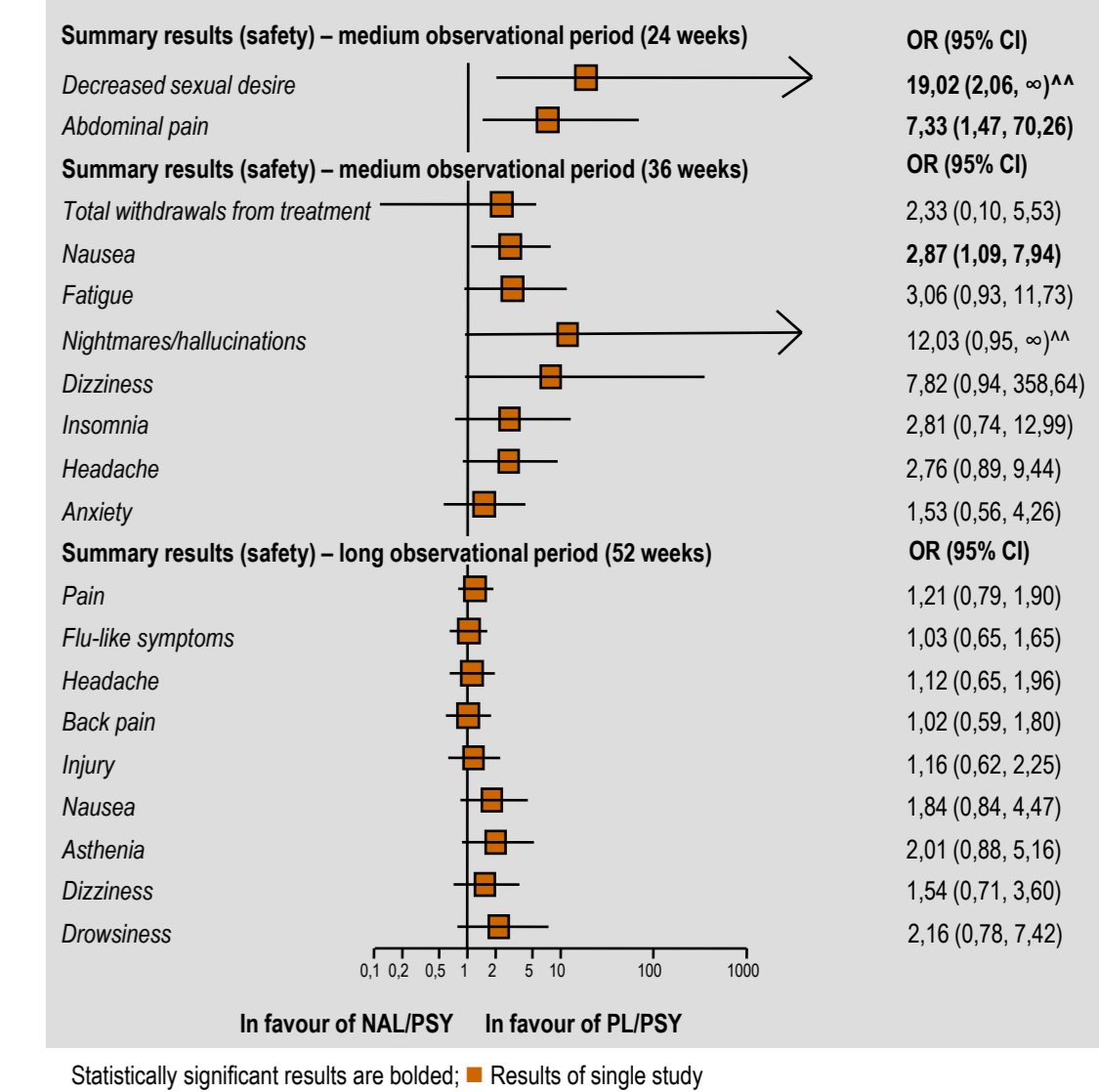
Statistically significant results are bolded; SMD-standardised mean difference; MD-mean difference; NNT-number needed to treat; NNH-number needed to harm; OR-odds ratio; CI-confidence interval, vs.-versus; GGT-gamma-glutamyl transpeptidase, ALT-alanine transaminase, AST-asparagine transferase, HDD-heavy drinking days.

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Statistically significant results are bolded; ♦ Result of meta-analysis, ■ Results of single study; *Calculated using the Peto method, **Calculated using the Mantel-Haenszel method with correction (M-H); AEs-adverse events



Statistically significant results are bolded; ■ Results of single study