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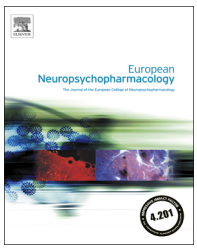

Differences in maintenance of response upon discontinuation across medication treatments in attention-deficit/hyperactivity disorder

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Abstract
The attention-deficit/hyperactivity disorder (ADHD) treatment literature has been focused on onset-of-effect and short-term effect size, with little exploration of ADHD symptoms upon medication discontinuation. The objective of this narrative review and analysis was to better understand the relapse of ADHD symptoms upon discontinuation of medication treatment in children, adolescents, and adults with ADHD who have responded to medication treatment and to explore differences among different medications in maintaining treatment response. Randomized withdrawal studies of dexmethylphenidate hydrochloride (*d*-MPH), methylphenidate modified-release (MPH-LA), lisdexamphetamine dimesylate (LDX), guanfacine extended-release (GXR), and atomoxetine (ATX) in both children/adolescents and adults with ADHD were reviewed. The percentage of relapse was significantly higher and the time-to-relapse significantly shorter with placebo compared to active treatment in patients who were previously stable on 5 weeks to 1 year of active treatment, suggesting clinically significant benefit with continued long-term pharmacotherapy. However, percentage of relapse at each time point studied after discontinuing stimulants and GXR appears substantially higher than observed when discontinuing ATX, suggesting longer maintenance of response after

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discontinuing ATX than after stimulants and GXR. Additionally, slope of relapse percentages over time appears to be more rapid with stimulants or GXR than with ATX. These differences in maintenance of response among ATX, GXR, and stimulants may reflect differences in mechanisms of action and persistence of the medication effect. Alternatively, they may be due to methodological differences, including study design and response/relapse definitions. Continued investigation is needed regarding factors that affect risk of symptom relapse upon discontinuation of pharmacotherapy.
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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic disorder, lasting from childhood into adulthood in approximately two-thirds of patients (Faraone et al., 2006; Goodman, 2013; Pliszka, 2007; Simon et al., 2009). The ADHD treatment literature has been focused on onset of effect and short-term efficacy effect size, but very little related to ADHD symptoms upon medication discontinuation has been explored. Treatment rates of ADHD decline sharply from childhood through young adulthood, but the functional impairment often persists (Robb and Findling, 2013). Patients who do continue treatment of ADHD may have planned or unplanned drug "*holidays*" (e.g., breaks from medication on weekends or over summer break from school or work). However, there is a lack of information about how long to continue treatment for patients who are responding to treatment and what should be expected upon medication discontinuation after long-term medication treatment in patients with ADHD. Therefore, maintenance of response and relapse upon discontinuation may be important issues to consider in ADHD treatment.

Until recently, little information about relapse of ADHD symptoms following discontinuation of treatment has been available. The most widely used pharmacological treatments for ADHD are the stimulants methylphenidate (MPH) and amphetamine, and nonstimulants atomoxetine (ATX), guanfacine, and clonidine (Kooij et al., 2010). Atomoxetine, a selective norepinephrine reuptake inhibitor, is a nonstimulant medication approved for the treatment of ADHD in pediatric and adult patients in many countries. Maintenance of response with ATX has been demonstrated in pediatric (Buitelaar et al., 2007; Michelson et al., 2004) and adult patients (Upadhyaya et al., 2013). Recent studies have also examined maintenance of response with stimulants (Arnold et al., 2004; Coghill et al., 2014) and the nonstimulant guanfacine (Newcorn et al., 2014) in pediatric patients, and with stimulants in adult patients (Biederman et al., 2010; Brams et al., 2012; Buitelaar et al., 2012; Huss et al., 2014). With the availability of these recent data, the maintenance of response and relapse with ATX and other medications can be explored.

The objective of this narrative review and analysis was to better understand the relapse of ADHD symptoms upon discontinuation of medication treatment in children, adolescents, and adults with ADHD who have responded to medication treatment and to explore differences among medications in maintaining treatment response.

2. Experimental procedures

This study consisted of a review of maintenance of response summary results in published studies in children, adolescents, and adults who responded to treatment with stimulants and nonstimulants (Table 1); and an exploratory analysis of data from ATX maintenance of response studies.

2.1. Literature review

The electronic databases Medline, PsycINFO, and Embase were searched for articles published between January 1980 and July 2014. This review analyzed maintenance of response studies in children/adolescents and adults after treatment with stimulants and nonstimulants. The following keywords were searched: ADHD, relapse, and withdrawal. Studies were limited to human, randomized, controlled trials published in peer-reviewed journals in English. The titles and abstracts of the articles obtained through this systematic literature search were screened for eligibility (48 total eligible abstracts were reviewed for inclusion; Supplemental Figure 1). Only those articles that examined maintenance of response in patients with ADHD after response to treatment with stimulants and nonstimulants were inspected in detail for inclusion.

Efficacy data were compiled from 9 maintenance clinical trials, 4 in children and 5 in adults, diagnosed with ADHD according to *Diagnostic and Statistical Manual of Mental Disorders (DSM), 3rd Edition (DSM-III) or 4th Edition (DSM-IV)* criteria. Trial characteristics, relapse rate percentages, and time-to-relapse in each study were examined. A summary of the studies including the characteristics of patients is provided in Table 1. Patient characteristics were similar between studies.

2.2. Studies in children and adolescents

In pediatric patients, 4 studies were identified – including one study each using ATX (Buitelaar et al., 2007; Michelson et al., 2004), lisdexamfetamine dimesylate (LDX) (Coghill et al., 2014), dexmethylphenidate hydrochloride (*d*-MPH) (Arnold et al., 2004), and guanfacine extended-release (GXR) (Newcorn et al., 2014) (Table 2).

The ATX study was a global multicenter study in children and adolescents who responded to an initial 12-week, open-label treatment with ATX (1.2–1.8 mg/kg/day) and were then randomized to continued ATX treatment or placebo for

Table 1 Summary of ADHD withdrawal studies – patient characteristics.

Study	*N*	Sites	Mean age (years)	Sex	ADHD subtype	Baseline at study entry ADHD-RS-IV total score	Baseline at randomization ADHD-RS-IV total score	Baseline at study entry CGI-S score	Baseline at randomization CGI-S score
Children/adolescents									
ATX (First randomization) (Michelson et al., 2004)	292 ATX 124 PBO	33	10.6 ATX 10.1 PBO	89.4% male ATX, 90.3% male PBO	73.1% Combined; 22.4% inattentive	41.3	15.8 ATX 15.7 PBO	5.2	2.3 ATX 2.2 PBO
ATX (second randomization) (Buitelaar et al., 2007)	81 ATX 82 PBO	33	10.7 ATX 11.0 PBO	88.9% male ATX, 90.2% male PBO	74.2% combined; 20.9% inattentive	41.0 ATX 40.7 PBO	13.4 ATX 12.5 PBO	-	-
LDX (Coghill et al., 2014)	276	51	10.9 average in open-label	76.8% male	80.8% combined; 16.7% inattentive	40.7	41.9 LDX 40.2 PBO	4.9	5.1 LDX 5.0 PBO
d-MPH (Arnold et al., 2004)	35 *d*-MPH 40 PBO	7(US only)	10 *d*-MPH	77.5% male PBO, 85.7% male *d*-MPH	80% Combined; 20% inattentive	-	-	-	-
GXR (Newcorn et al., 2014)	157 GXR 15 PBO	67	10.7 GXR 11.0 PBO	74.3% male	84.1% combined; 12.1 inattentive	43.7	43.5	-	-
Adults									
ATX (Upadhyaya et al., 2013)	524	152	33.1 average	58.4% male	72.3% Combined; 25.4% inattentive	-	-	5.0	4.99
MPH-LA (Huss et al., 2014)	725	67	35.4 average	54.5% male	-	39.2	-	-	-
LDX (Brams et al., 2012)	116	36 (US only)	35.8 average	43.1% male	-	11.2[a]	10.6	2.1[a]	2.1
OROS-MPH (Biederman et al., 2010)	112 OROS-MPH 115 PBO	1(US)	34.7 OROS-MPH 36.4 PBO	52% male	-	-	-	-	-
OROS-MPH (Buitelaar et al., 2012)	155 OROS-MPH	23 (European countries)	35.0 OROS-MPH, open-label	54% male	68.4% Combined; 27.7% inattentive	-	-	-	-

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale; ATX, atomoxetine; CGI-S, Clinical Global Impression of Severity scale; GXR, guanfacine extended-release; LDX, lisdexamfetamine dimesylate; *d*-MPH, dexmethylphenidate hydrochloride; MPH-LA, methylphenidate modified-release; OROS-MPH, osmotic-release oral system methylphenidate; PBO, placebo; US, United States; -, not available.

[a]At baseline patients were to have had a ADHD-RS-IV scale with Adult Prompts Total Score <22. Participants were required to have received commercially available LDX (30, 50, or 70 mg/day) for ≥ 6 months with an acceptable safety profile.

Table 2 Summary of ADHD pediatric withdrawal studies – response and relapse definitions and outcomes.

Study	Lead-in period	Response cutoff	Maintenance of response period	Primary outcome	Relapse definition	Relapse rate upon medication discontinuation (%)	Relapse rate with medication maintenance (%)
ATX (First randomization) (Michelson et al., 2004)	12-Week (10-week open-label) (n=604)	ADHD-RS-IV total score $\geq$25% ↓, and CGI-S score of 1 or 2 at both 9 and 10 weeks	9-Month double-blind (n=416)	Time-to-relapse over first 9 months. PBO=146 days; ATX=218 days	Primary-↑to 90% of ADHD-RS-IV total score at study entry and $\geq$2-point↑in CGI-S score at the end of the 10-week treatment period. secondary- $\geq$50%↑in ADHD-RS-IV total score and $\geq$2-point↑in CGI-S compared to randomization	Primary 37.9%; secondary 47.6%	Primary 22.3%; secondary 28.4%
ATX (second randomization) (Buitelaar et al., 2007)	~1-Year (n=292)	$\geq$25%↓in ADHD-RS-IV total score, and CGI-S score of 1 or 2 after 10 weeks	6-Month double-blind (n=163)	Time-to-relapse for all randomized subjects. PBO=130.8 days; ATX=160.5 days	Primary-↑to 90% of ADHD-RS-IV total score at study entry and $\geq$2-point↑in CGI-S score at the end of the 10-week treatment period. Secondary- $\geq$50%↑in ADHD-RS-IV total score and $\geq$2-point↑in CGI-S score compared with scores at the time of second randomization	Primary 12.2%; secondary 19.5%	Primary 2.5%; secondary 7.4%
LDX (Coghill et al., 2014)	26-Week open-label (n=276)	Final 2 weeks of open-label patients discontinued if dose adjustments needed, experienced unacceptable AEs, or had an ADHD-RS-IV total score >22 or CGI-S score $\geq$3	6-Week double-blind (n=157)	Percentage of treatment failures	$\geq$50%↑in ADHD-RS-IV total score and $\geq$2-point↑in CGI-S score compared to randomization-withdrawal period	Primary 67.5%	Primary 15.8%
d-MPH (Arnold et al., 2004)	6-Week open-label phase (n=89)	Stable dose and CGI-I score of 1 or 2 for final 2 weeks of open-label	2-Week double-blind (n=76)	Percentage of treatment failures	Primary-treatment failures, defined as CGI-I score of 6 or 7 relative to visit 8. secondary-treatment failure CGI-I score=5, 6, or 7	Primary 61.5%; secondary 71.8%	Primary 17.1%; secondary 45.8%
GXR (Newcorn et al., 2014)	7-Week open-label dose-optimization, 6-week open-label maintenance of optimized dose (n=528)	$\geq$30%↓from visit 2/enrollment in the ADHD-RS-IV total score and a CGI-S score of 1 or 2 with tolerable side effects	26-Week double-blind, RWP (n=316)	Percentage of treatment failures	$\geq$50%↑in ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score from RWP baseline (visit/week 13) at 2 consecutive visits	Primary 64.9%	Primary 49.3%

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale; AEs, adverse events; ATX, atomoxetine; CGI-I, Clinical Global Impression of Improvement scale; CGI-S, Clinical Global Impression of Severity scale; GXR, guanfacine extended-release; LDX, lisdexamfetamine dimesylate; *d*-MPH, dexmethylphenidate hydrochloride; n, number of patients; PBO, placebo; RWP, randomized withdrawal phase; ↓, decrease; ↑, increase.

9 months under double-blind conditions (first randomization) (Michelson et al., 2004). Subjects who maintained their response to ATX acutely and had completed 1 year of ATX treatment were re-randomized in double-blind fashion to continued ATX or to placebo substitution for 6 months (second randomization) (Buitelaar et al., 2007). In Buitelaar et al. (2007) and Michelson et al. (2004), relapse was defined as an increase in ADHD Rating Scale [ADHD-RS-IV] total score to $\geq$90% of the score at study entry and an increase of $\geq$2 points in Clinical Global Impression of Severity (CGI-S) score above the CGI-S score at the end of the initial 10-week treatment period.

A 26-week, open-label, phase 3 trial evaluated the efficacy and safety of LDX (30, 50, or 70 mg per day) in patients with ADHD (6–17 years; N=276) from Europe and the United States (Coghill et al., 2014). Patients who completed open-label treatment (n=157) were randomized 1:1 to their optimized dose of LDX (30, 50, or 70 mg/day) or placebo for a 6-week, randomized withdrawal phase. Relapse was defined as a $\geq$50% increase in the ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score relative to the start of the randomized withdrawal phase.

Relapse rates in children with ADHD were also analyzed after treatment with *d*-MPH (Arnold et al., 2004). After a 6-week, open-label titration of *d*-MPH (2.5–10.0 mg twice-daily), relapse was assessed during a randomized, double-blind, placebo-controlled, 2-week withdrawal period. The study took place at 7 sites in the United States. Relapse was defined as treatment failure based on scores of 6 or 7 on the Clinical Global Impression of Improvement scale (CGI-I) compared to randomization.

The long-term maintenance of efficacy of GXR (4–7 mg/day) was studied in children and adolescents (6–17 years) with ADHD (ADHD-RS-IV total score $\geq$32 and CGI-S score $\geq$4) (Newcorn et al., 2014) in a multicenter, double-blind, placebo-controlled, randomized withdrawal study. The study was conducted at 67 centers in Europe, the United States, and Canada between May 2010 and June 2013. The study comprised 6 time periods: screening and washout; 7-week, open-label, dose-optimization; 6-week, open-label, maintenance of optimized dose; 26-week, double-blind, randomized withdrawal phase; 2-week, posttreatment taper; and 1-week, safety follow-up. Study drug (1, 2, 3, or 4 mg GXR) was administered once-daily; treatment failure was defined as a $\geq$50% increase in ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score at 2 consecutive visits, compared with respective scores at the double-blind baseline visit (visit 13/week 13), or discontinuation for any reason.

2.3. Studies in adults

In adult patients, studies examining ATX (Upadhyaya et al., 2013), MPH modified-release (MPH-LA) (Huss et al., 2014), LDX (Brams et al., 2012), or osmotic-release oral system methylphenidate (OROS-MPH) (Biederman et al., 2010; Buitelaar et al., 2012) were identified (Table 3).

Maintenance of response with ATX treatment was analyzed in adults with ADHD during a 25-week, double-blind, placebo-controlled, randomized withdrawal phase (Upadhyaya et al., 2013). Only adults who previously responded to 12-week, open-label treatment with ATX and maintained that response during a randomized, 12-week, double-blind maintenance period (ATX dose: 80–100 mg/day) were included in the study. The study was conducted at 152 sites in the European Union (60%), United States, Mexico, Argentina, and Russia. Relapse was defined as a return to $\geq$80% of open-label, baseline Conners' Adult ADHD Rating Scale-Investigator-Rated: Screening Version (CAARS-Inv:SV) total score after 24 weeks and 2 consecutive visits with a CGI-S score $\geq$4 points.

The maintenance of effect of MPH-LA in adults with ADHD was evaluated in a 40-week, double-blind, randomized, placebo-controlled study. The study was conducted at 67 centers in 9 countries. The study consisted of 3 treatment phases: (1) a 9-week, double-blind, randomized, placebo-controlled, parallel-group, confirmation phase, (2) a 5-week, real-life dose, optimization phase during which all patients, including those treated with placebo in the double-blind dose-confirmation phase, were started on a dose of 20 mg/day and titrated each week to their optimal dose, and (3) a 6-month, double-blind, randomized, placebo-controlled, withdrawal phase to evaluate the maintenance of effect of MPH-LA (40, 60, or 80 mg/day) in adults with ADHD (Huss et al., 2014). Relapse was defined as a $\geq$30% worsening from randomization and $<$30% remaining improvement from ADHD-RS-IV total score at study entry.

The maintenance of effect of LDX (30, 50, or 70 mg/day) was examined in a double-blind, multicenter, placebo-controlled, randomized withdrawal study consisting of 4 phases (Brams et al., 2012). The study was conducted at 36 sites in the United States. At the end of the open-label treatment phase, participants entered a 6-week, double-blind, randomized, withdrawal phase and were assigned to treatment with LDX or placebo. Relapse was defined as a $\geq$50% increase in ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score.

The maintenance of effect of OROS-MPH was examined in 2 studies (Biederman et al., 2010; Buitelaar et al., 2012). The first study was a 3-phase, double-blind, placebo-controlled, parallel study in adult patients with ADHD, (Biederman et al., 2010) containing a 6-week, acute efficacy phase (mean daily dose: OROS-MPH 0.97$\pm$0.32 mg/kg), followed by a 24-week, double-blind, continuation phase for treatment responders, and a 4-week, double-blind, placebo-controlled, discontinuation phase. The study was conducted at a site in the United States. Relapse was defined as a $\geq$2-point increase in CGI-I score from the end of acute treatment or $<$15% improvement on the Adult ADHD Investigator Symptom Rating Scale (AISRS) for 2 consecutive visits.

In the second study, OROS-MPH (18, 36, 54, or 72 mg/day) was evaluated open-label for 52 weeks in patients who had previously completed a short-term, placebo-controlled trial and a short-term, open-label extension (Buitelaar et al., 2012). The study was conducted at 23 European sites. Patients completing 52 weeks of treatment were eligible for a 4-week, placebo-controlled, randomized withdrawal phase in which loss of treatment effect was assessed using the Conners' Adult ADHD Rating Scale-Observer-Rated: Screening Version (CAARS-O:SV) and CGI-S scores. Relapse was defined as an increase (worsening) of $>$50% from baseline in CAARS-O:SV total score or a $\geq$2-point increase in CGI-S score from randomization.

Table 3 Summary of ADHD adult withdrawal studies – response and relapse definitions and outcomes.

Study	Lead-in period	Response cutoff	Maintenance of response period	Primary outcome	Relapse definition	Relapse rate upon medication discontinuation (%)	Relapse rate with medication maintenance (%)
ATX (Upadhyaya et al., 2013)	24-Week (12 weeks open-label followed by 12 weeks of maintenance)(n=2017)	≥30% Improvement in CAARS-Inv-SV total score and CGI-S score ≤3 maintained through the maintenance phase (1 excursion allowed)	25-Week double-blind, RWP (n=524)	Maintenance of response (% with↓≥30% baseline CAARS-Inv-SV total score and CGI-S score ≤3 (2 nonconsecutive excursions allowed)	2 Consecutive visits with CGI-S score ≥4 and return to ≥80% of original baseline CAARS-Inv-SV total score	Primary 7.4%	Primary 2.3%
MPH-LA (Huss et al., 2014)	5–14 Weeks (9-week PBO-controlled, double-blind period of 3 doses followed by 5-week period of patients' doses titrated to optimal dose with at least 1-week stable dose)(n=725)	≥30% ↓ADHD-RS-IV total score by end of 5-week dose-optimization phase	6-Month double-blind (n=489)	% Treatment failure using logistic regression	≥30% Worsening from randomization and <30% remaining improvement from original baseline on ADHD-RS-IV total score	Primary 49.6%	Primary 21.3%
LDX (Brams et al., 2012)	Retrospective 6-month period and prospective 3-week open-label period (n=123)	Stable dose in retrospective and prospective periods. Patients who had AHDH-RS-IV score ≥22 or CGI-S score >3 at visit 3 were withdrawn from the study.	6-week double-blind (n=116)	Rate of relapse	50%↑in ADHD-RS-IV total score and ≥2-point↑in CGI-S score	Primary 75.0%	Primary 8.9%
OROS-MPH (Biederman et al., 2010)[a]	6-Week PBO-controlled double-blind efficacy, responders 24 week double-blind maintenance (n=227)	CGI-I score ≤2 and AISRS↑>30% from baseline	4-Week double-blind (n=23)	Rate of relapse	CGI-I score ≥2-point↑from the end of phase 1 or <15% improvement on AISRS for 2 consecutive visits	Primary 18%	Primary 0%
OROS-MPH (Buitelaar et al., 2012)	5-Week double-blind PBO-controlled study (n=355) followed by open-label OROS-MPH for minimum exposure of 52 weeks (n=155)	Completers of initial 7-week open-label phase and those with 4 weeks stable dose at end of open-label	4-Week double-blind RWP (n=45, 99 completed the open-label, but only 45 consented)	Worsening in mean CAARS-O:SV score. Not significant. Both arms had mean worsening from baseline.	Primary:↑(worsening) of >50% from baseline in CAARS-O:SV total score. Secondary: ≥2-point↑in CGI-S score from randomization or discontinued for lack of efficacy	Primary 36.4% secondary ~41%	Primary 26.1% secondary ~25%

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale; AISRS, Adult ADHD Investigator Symptom Rating Scale; ATX, atomoxetine; CAARS-Inv:SV, Conners' Adult ADHD Rating Scale-Investigator-Rated: Screening Version; CAARS-O:SV, Conners' Adult ADHD Rating Scale-Observer-Rated: Screening Version; CGI-I, Clinical Global Impression of Improvement scale; CGI-S, Clinical Global Impression of Severity scale; LDX, lisdexamfetamine dimesylate; MPH-LA, methylphenidate modified-release; n, number of patients; OROS-MPH, osmotic-release oral system methylphenidate; PBO, placebo; RWP, randomized withdrawal phase; ↓, decrease; ↑, increase.

[a]Not included in the current analyses because did not demonstrate maintenance of response.

The OROS-MPH studies were not included in the current analysis, as they were not able to demonstrate maintenance of response (Biederman et al., 2010; Buitelaar et al., 2012).

2.4. Statistical analyses

Data from ATX studies – in children and adolescents (Buitelaar et al., 2007; Michelson et al., 2004) and in adults (Upadhyaya et al., 2013) – were analyzed. The primary definition of relapse in the study of children and adolescents treated with ATX was an increase to 90% of ADHD-RS-IV total score at study entry and a $\geq$2-point increase in CGI-S score. The primary definition of relapse used in the adult study of ATX was 2 consecutive visits with a CGI-S score of $\geq$4 and return to $\geq$80% of original baseline CAARS-Inv:SV total score. As shown in Tables 2 and 3, the definition of relapse varied among studies. Hence, for appropriate indirect comparison in children and adolescents, ATX data were re-analyzed according to a *post-hoc* definition of relapse that most closely mirrored those in stimulant and guanfacine trials ($\geq$50% increase in ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score from randomization observed at 1 visit). This *post-hoc* definition of relapse is referred to as a secondary definition of relapse.

Time-to-relapse was analyzed in the ATX trials using Kaplan–Meier survival analysis and compared between groups using the Wilcoxon test (for the ATX study in children and adolescents) and the log-rank test (for the ATX study in adults). The Wilcoxon test was planned for the ATX study in children and adolescents because it was the first relapse prevention ATX trial (Michelson et al., 2004) and it was expected at the time that relapse would occur earlier rather than later, which was an appropriate assumption for the Wilcoxon test. For the ATX study in adults (Upadhyaya et al., 2013), based on the observations from the study in children and adolescents, the log-rank test was specified to require less assumption of the type of relapse patterns that would be observed.

3. Results

3.1. Studies in children and adolescents

A summary of ADHD pediatric withdrawal studies' response and relapse definitions and outcomes are shown in Table 2. In the ATX trial, relapse upon discontinuation, defined as a return to 90% of baseline ADHD-RS-IV total score at study entry and a $\geq$2-point increase in CGI-S score, was seen in 37.9% of patients in the first randomization (9-month double-blind phase) and 12.2% of patients in the second randomization (6-month double-blind continuation). When relapse was defined as a $\geq$50% increase in ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score compared to first and second randomization, relapse upon discontinuation was seen in 47.6% of patients in the ATX trial first randomization (after responding to ATX for 10 weeks) and 19.5% of patients in the second randomization (after responding to ATX for almost 1 year). In the LDX trial, 67.5% of patients showed relapse 6 weeks after discontinuation. In the *d*-MPH trial, 61.5% of patients showed relapse defined as a CGI-I score of 6 or 7 relative to visit 8, after responding to *d*-MPH for 6 weeks, and 71.8% of patients showed relapse defined as a CGI-I score of 5, 6, or 7, after the 2-week withdrawal phase. In the GXR trial, 64.9% of patients showed relapse after responding to GXR for 13 weeks.

Relapse rates upon medication discontinuation in children previously responsive and stable on treatment are shown in Figure 1. The percentage of children and adolescents relapsing after approximately 1 year of ATX treatment is shown in Figure 2; relapse is defined as a $\geq$50% increase in ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score. A gradual increase in relapse over time (25 weeks or 180 days) was observed.

3.2. Studies in adults

A summary of ADHD adult withdrawal studies' response and relapse definitions and outcomes is shown in Table 3. In the ATX trial, relapse upon discontinuation was defined as 2 consecutive visits with a CGI-S score $\geq$4 and a return to $\geq$80% of original baseline CAARS-Inv:SV total score. Relapse upon discontinuation was seen in 7.4% of patients 25 weeks after discontinuation. In the MPH-LA trial, after a 6-month discontinuation, 49.6% of patients showed relapse upon discontinuation, defined as $\geq$30% worsening from randomization and $<$30% remaining improvement from ADHD-RS-IV total score at study entry. In the LDX trial, relapse was defined as a $\geq$50% increase in ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S score, and relapse was seen in 75.0% of patients 6 weeks after discontinuation.

Relapse upon medication discontinuation in adults previously responsive and stable on ATX or stimulant treatment is shown in Figure 3. The percentage of patients relapsing after approximately 25 weeks of ATX treatment is shown in Figure 4; relapse is defined as a $\geq$30% increase in CAARS-Inv:SV total score. Over time (180 days) the percentage of patients relapsing steadily increased for placebo compared to ATX.

4. Discussion

Treatment with ATX (among patients who previously responded to medication) was associated with a low rate of relapse after discontinuation of treatment. Persistent symptom relief, even upon treatment discontinuation, may be the result of lasting neurobiological changes and/or behavioral changes associated with consolidation of treatment effects (Fumagalli et al., 2010; Udvardi et al., 2013).

In a study of the rat brain, 2 months after final drug exposure, ATX was shown to affect transcription/translation of the N-methyl-D-aspartate (NMDA) receptor and the norepinephrine transporter in vivo (Udvardi et al., 2013). In adolescent spontaneously hypertensive rats, subchronic exposure to ATX was shown to increase brain-derived neurotrophic factor (BDNF) expression and signaling in the prefrontal cortex, whereas MPH reduced it. In addition, MPH but not ATX increased BDNF messenger RNA in the striatum and nucleus accumbens (Fumagalli et al., 2010).

The data presented here raise the possibility of differences in the neurobiological effects of stimulants and ATX in humans (both adults and children) as well (Bush et al., 2013;

Schulz et al., 2012). Regional similarities and differences in the way stimulants and ATX affect brain activity in adults after 6 weeks of treatment have been shown with functional magnetic resonance imaging (fMRI) (Bush et al., 2013). Both stimulants and ATX significantly increased activation in cortical and subcortical regions that subserve attention and executive function. However, activation of the dorsal anterior cingulate cortex was unique to ATX, and activation of the striatum was unique to MPH. These differential effects could potentially contribute to the differences in relapse seen across treatment types, but the specific manner in which differential activation of brain regions leads to these clinical changes is not clear. Interestingly, even though both MPH and ATX were associated with similar improvements in ADHD symptoms and response inhibition on the go/no-go test, there were differential activations in the right inferior frontal gyrus, left anterior cingulate, supplementary motor area, and bilateral posterior cingulate cortex (Schulz et al, 2012).

In a fMRI study with healthy volunteers who received a single dose of MPH or ATX before performing a rewarded working memory task, MPH and ATX had differential effects on activated and deactivated networks, although the effects of MPH and ATX were qualitatively similar (Marquand et al., 2011). MPH produced greater activity in working memory networks (the ability to hold and manipulate information for future action), and ATX produced greater activity in the default mode network. MPH enhanced task-related deactivations more than ATX, whereas ATX attenuated working memory networks more than MPH. Thus, interactions between drug effects and motivational state may be important in defining the effects of MPH and ATX.

The initial response definition was different among studies, and the studies used different definitions of relapse. We tried to correct for the differences in relapse definitions by reanalyzing the ATX studies in a manner that was similar to the stimulant and GXR studies. The length of the withdrawal period was the same or longer for ATX compared with the stimulant and GXR studies.

4.1. Clinical implications

In general, continuous treatment of ADHD is recommended; for patients who have treatment response for a short time, treatment should be continued as long as it remains clinically effective (National Institute for Health and Clinical Excellence [NICE], 2008). In patients who are stable, treatment should be reviewed annually, assessing clinical need, benefits, and side effects. In patients who did not have severe problems at baseline (e.g., legal problems, history of severe impulsivity) that could become worse upon

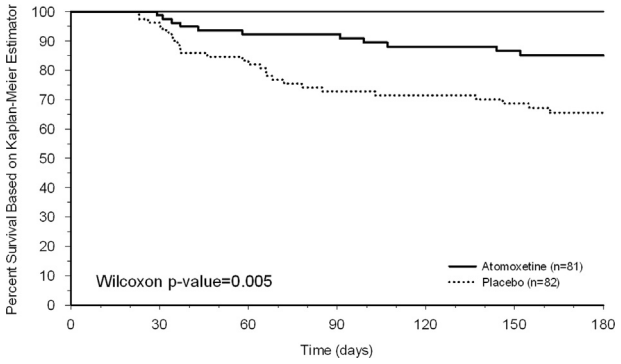

Figure 2 Long-term ADHD relapse prevention study in children and adolescents: relapse after approximately 1 year of atomoxetine treatment. The graph shows data up to 25 weeks (approximately 180 days). The mean days to relapse were 171 days for atomoxetine and 146 days for placebo. Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

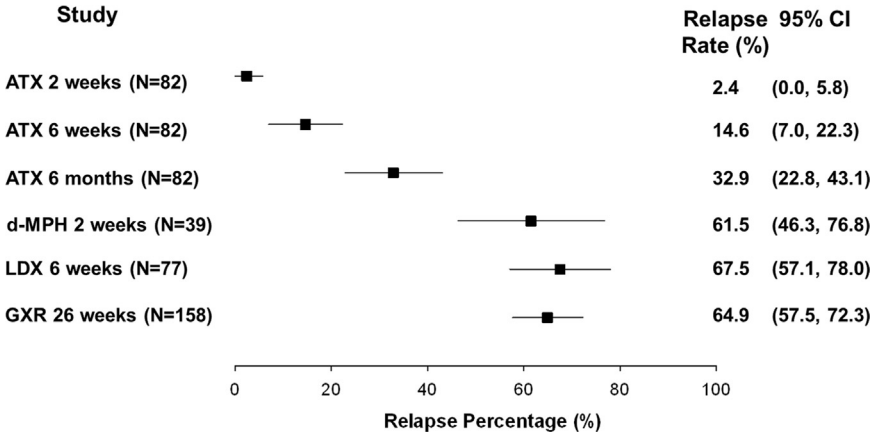

Figure 1 Relapse upon medication discontinuation in children previously responsive and stable on long-term atomoxetine or stimulant treatment. Relapse was defined as an increase to 50% of ADHD-RS-IV total score and a $\geq$2-point increase in CGI-S compared to randomization. ATX data were re-analyzed and patients had to meet relapse criteria at 1 visit (in Buitelaar et al., 2007; patients had to meet identical relapse criteria at 2 consecutive visits). ATX (2-week, n=2; 6-week, n=12; 6-month withdrawal period, n=27); *d*-MPH (2-week withdrawal period, n=24); LDX (6-week withdrawal period, n=52); GXR (26-week withdrawal period, n=98). The data are from the following distinct studies: *d*-MPH (Arnold et al., 2004); GXR (Newcorn et al., 2014); LDX (Coghill et al., 2014); ATX (Buitelaar et al., 2007; Michelson et al., 2004). Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale; ATX, atomoxetine; CGI-S, Clinical Global Impression of Severity scale; CI, confidence interval; GXR, guanfacine extended-release; LDX, lisdexamphetamine dimesylate; *d*-MPH, dexmethylphenidate hydrochloride.

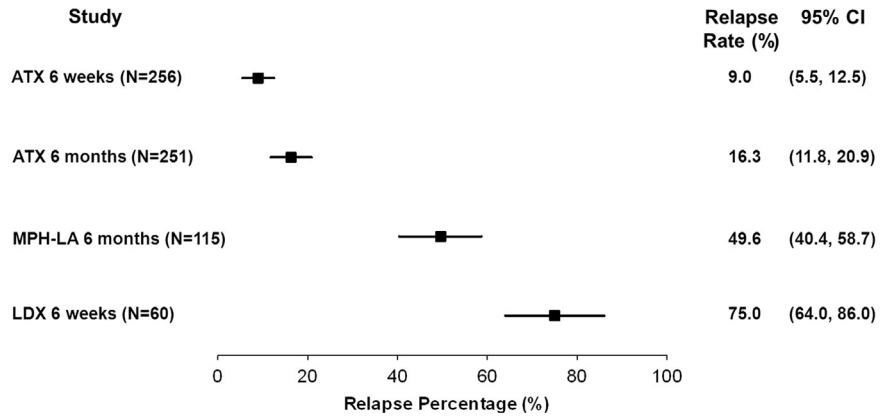

Figure 3 Relapse upon medication discontinuation in adults previously responsive and stable on long-term atomoxetine or stimulant treatment. Relapse defined as an increase to 50% of CAARS-Inv:SV total score and a $\geq$2-point increase in CGI-S score compared to randomization. The labeling indicates the length of the withdrawal period after stopping the referenced medication. ATX (6-week withdrawal period, n=23; 6-month withdrawal period, n=41); MPH-LA (6-month withdrawal period, n=57); LDX (6-week withdrawal period, n=45). The data are from the following distinct studies: MPH-LA (Huss et al., 2014); LDX (Brams et al., 2012); ATX (Upadhyaya et al., 2013). Abbreviations: ATX, atomoxetine; CAARS-Inv:SV, Conners' Adult ADHD Rating Scale-Investigator-Rated: Screening Version; CGI-S, Clinical Global Impression of Severity scale; CI, confidence interval; LDX, lisdexamphetamine dimesylate; MPH-LA, methylphenidate modified-release.

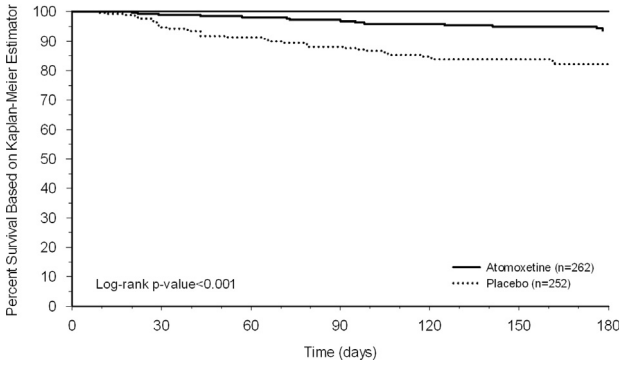

Figure 4 ADHD maintenance of response (withdrawal) study in adults: relapse after approximately 24 weeks of atomoxetine treatment. The graph shows data up to 25 weeks (approximately 180 days).

treatment discontinuation, the need for continuing treatment should be periodically assessed, as indicated in the United Kingdom summary of product characteristics for ATX (Eli Lilly and Company Limited, 2013).

When making treatment decisions about patients who are responding well to treatment, it is important to set accurate expectations after discontinuation. If patients decide to discontinue, they should continue to be evaluated to assess initial relapse symptoms.

The differences in the mechanism of action between stimulants and ATX may lead to a lower percentage of relapse upon discontinuation of treatment with ATX. Onset of efficacy may be slower with ATX compared with stimulants; however, responders (after long-term maintenance) may be able to maintain response upon discontinuation much longer. In Figures 2 and 4 the percentage of patients relapsing slowly increases over time compared to the relapse patterns seen with other stimulant and nonstimulant medications which increase quickly after discontinuation (Brams et al., 2012; Coghill et al., 2014; Newcorn et al., 2014). This effect may be due to more than the gradual ATX offset of effect, because relapse upon discontinuation tends to happen beyond the 12-week mark. Atomoxetine may be unique even among nonstimulants, considering that GXR, another nonstimulant, appears to have a higher percentage of relapse and a more rapid relapse rate, which are more similar to stimulant medication.

4.2. Limitations

The following limitations need to be considered when interpreting the data presented here. No head-to-head comparisons were performed, and differences across study populations included geography, ethnicity, comorbidity, and duration of disorder. Unknown study design effects are a potential limitation, and design differences among studies were present (e.g., duration of the study, definition of relapse, length of withdrawal period, initial response definition, time of lead-in period). Comparisons here are made between long-term treatment with ATX and a mixture of long-term and shorter-term treatments with stimulants and GXR, and these differences in treatment time before medication withdrawal can influence the reported relapse rates. In addition to differences in the neurobiological effects of stimulants and ATX, several possible factors related to the clinical trials may have contributed to the differences in observed percentages of relapse for ATX versus stimulants. Patient population differences among the studies can contribute to the observed differences (i.e., studies differed in the geography, ethnicity, comorbidity, and duration of the disorder). In studies with stimulants, due to quicker onset, the patients may “feel” a stimulant more (including withdrawal) which may cause the time-to-randomization not to be truly blind. The duration of the study and the availability of other treatments could also affect the outcome of the study. It is possible that the population of responders in the ATX studies includes a

higher than expected percentage of (unknown/hidden) placebo responders giving rise to low relapse percentages. Additionally, the ATX study in adults examined relapse in a highly selected subpopulation that responded to treatment with ATX and was compliant with the lengthy study protocol. Patients who responded poorly to treatment with ATX and displayed fewer behavioral adaptations before randomization might have displayed higher relapse rates after discontinuation of treatment with ATX, but these patients were likely eliminated from the study due to the response criteria that had to be met before re-randomization for the withdrawal phase. Another explanation could be that there is an increased unintentional "unblinding" of stimulants due to more obvious immediate effects, although this is not sufficient to explain such large differences over the long duration of the ATX studies.

4.3. Conclusion

The percentage of relapse at each time point studied after discontinuing stimulants and GXR appears substantially higher than observed when discontinuing ATX, suggesting longer maintenance of response after discontinuing ATX than after stimulants and GXR. When these results for ATX are viewed in the context of results for other medications, it is important to consider whether differences in mechanism of action may lead to differential effects at time of treatment discontinuation. In addition, relapse over time appears more rapid for discontinuation from stimulants and GXR, and more gradual for discontinuation from ATX. Additional research, including head to head studies, are needed to better understand the relapse of ADHD symptoms and the neurobiological basis of relapse after medication discontinuation.

Role of funding source

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Contributors

Himanshu Upadhyaya and Virginia Haynes managed the literature searches and analyses. Yoko Tanaka undertook the statistical analysis, and Himanshu Upadhyaya wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Jan Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties.

Philip Asherson has acted in an advisory role for Shire, Janssen-Cilag, Eli Lilly and Flynn Pharma. He has received education or research grants from Shire, Janssen-Cilag and Eli Lilly. He has given talks at educational events sponsored by the above companies.

Cesar Soutullo has participated in advisory boards, received speaker's honoraria or participated in research studies within the last 5 years with Alicia Koplowitz Foundation, Editorial Médica Panamericana, Eli Lilly, EUNSA [University of Navarra Press], Fundación Caja Navarra, Janssen, Mayo Ediciones, Medice/Juste, Rubiò, Shire, Sociedad Vasco-Navarra Psiquiatría, University of Navarra Research Projects [PIUNA] and Wolters Kluwer.

Michael Colla has participated in advisory boards, received speaker's honoraria or participated in Phase-III-studies within the last 3 years with Shire, Eli Lilly, and Novartis.

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Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2015.06.003.

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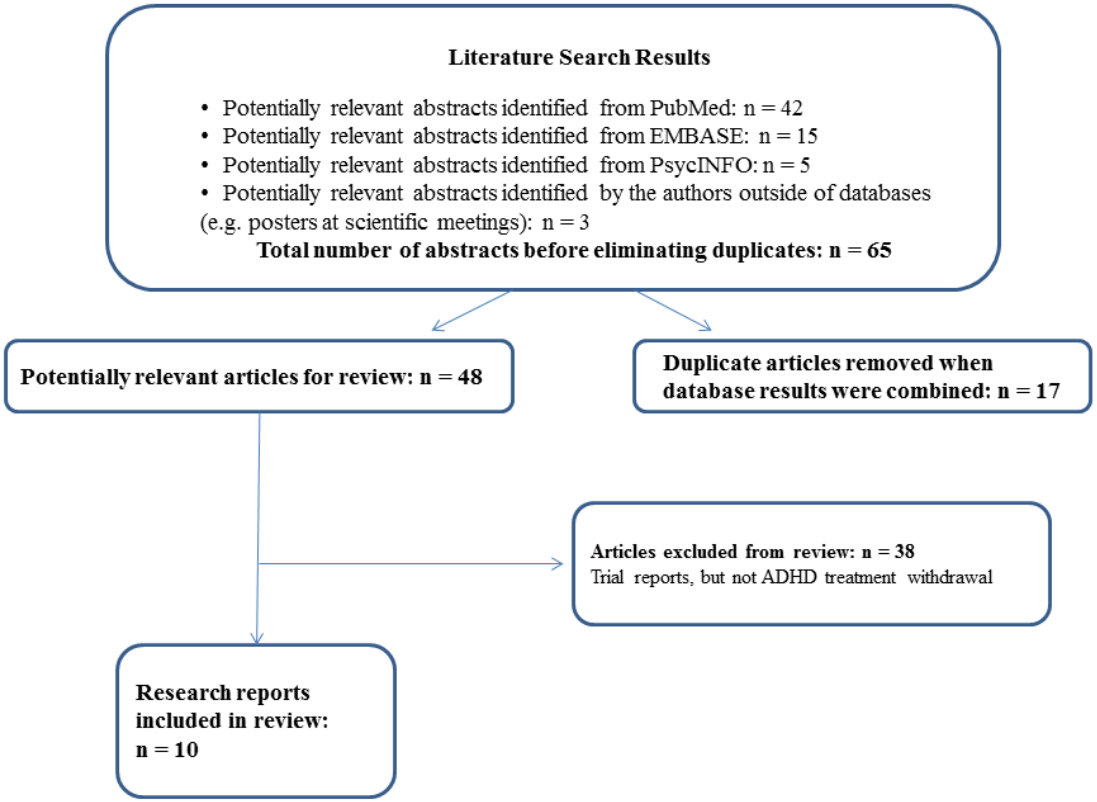
Supplemental Material

Supplemental Figure 1. Summary of Literature Review Results



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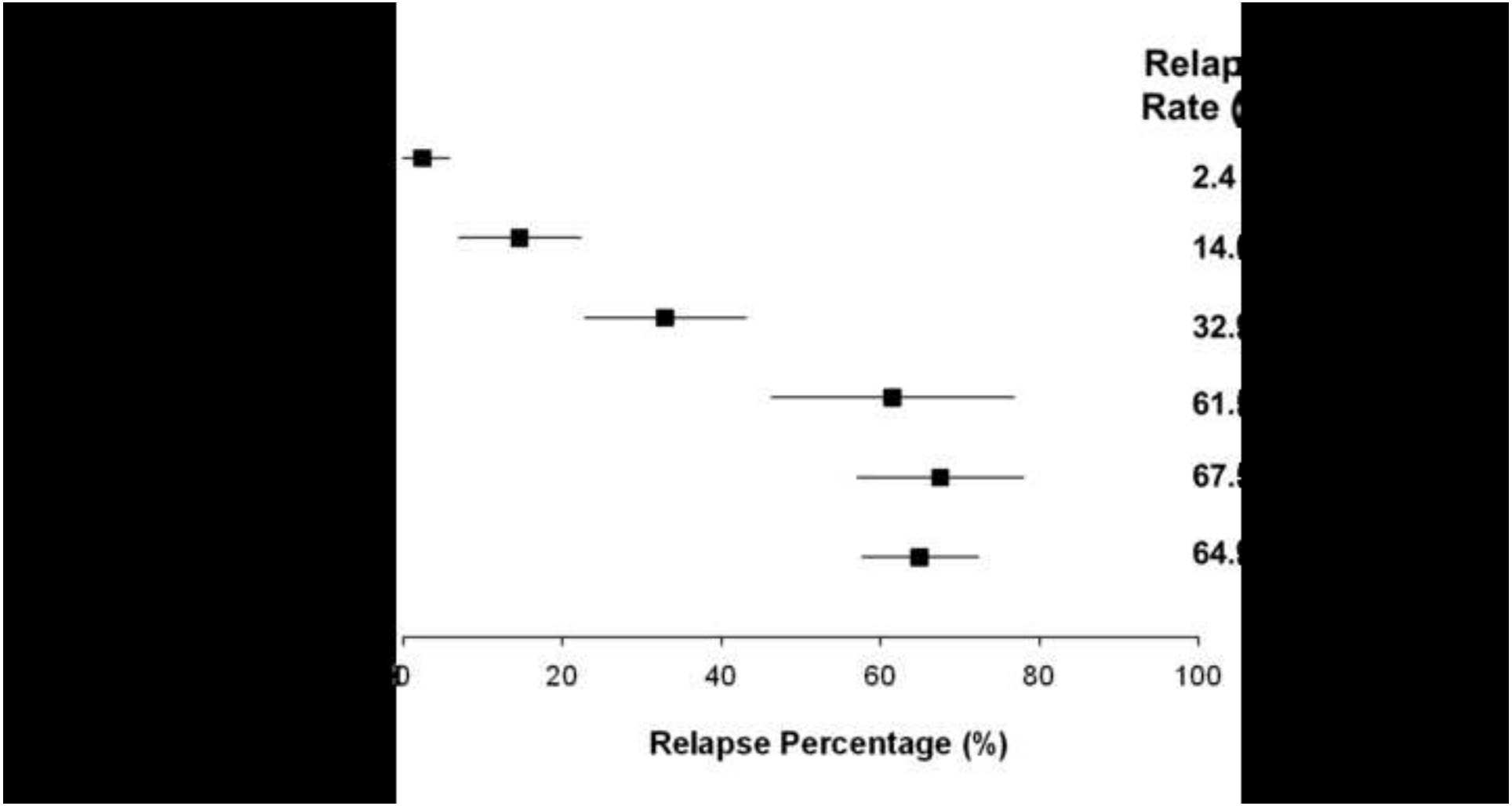

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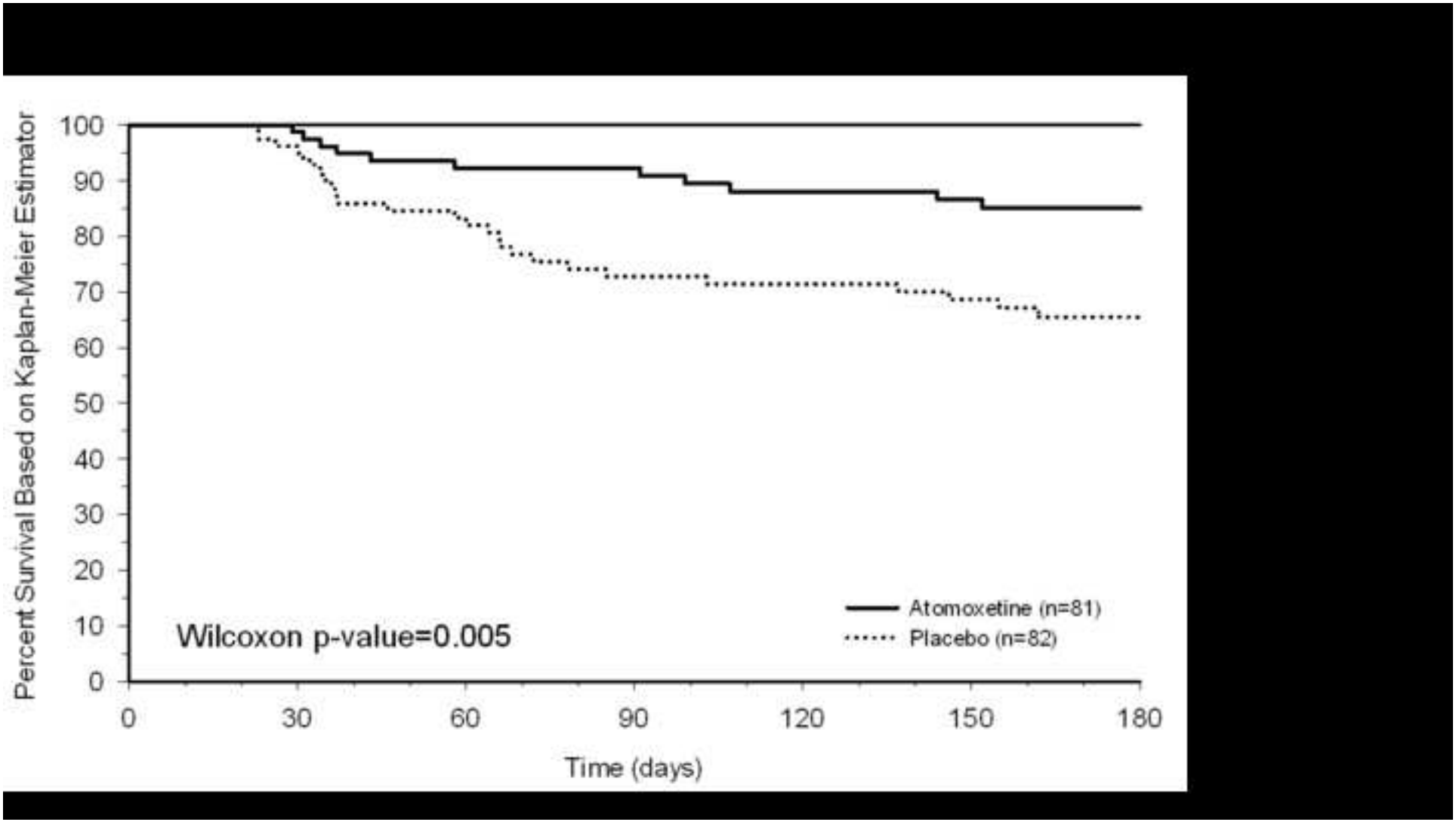

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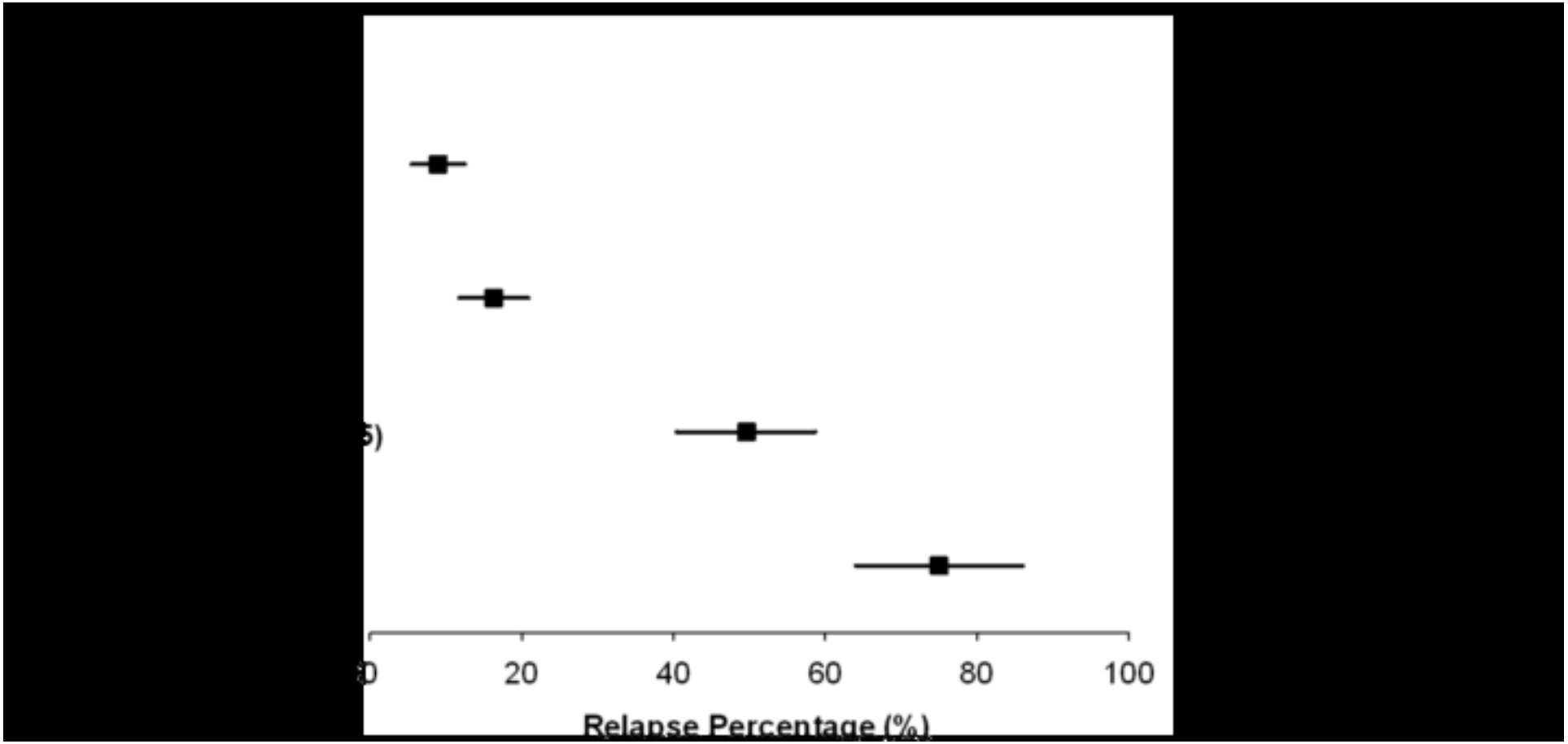

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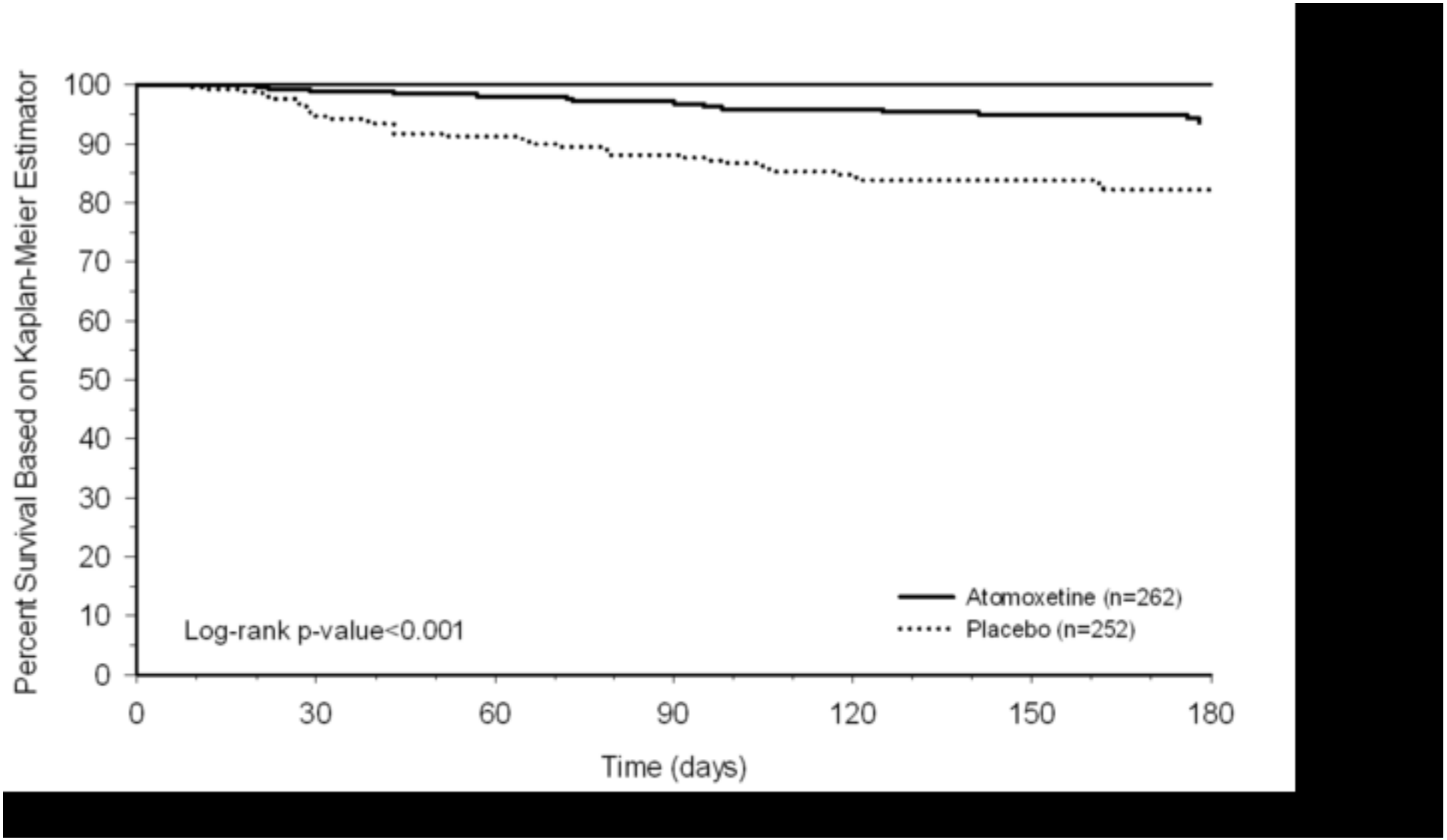
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