**Table 1.** Studies on the side effects of methylphenidate in adults diagnosed with ADHD. The risk of bias and study quality assessed with the Effective Public Health Practice Project’s Quality Assessment Tool for Quantitative Studies (QATQS) was presented as the global rating for each publication (1 - strong, 2 - moderate, 3 - weak).

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| AUTHOR | YEAR | TYPE OF STUDY | DURATION | MPH | AGE | NUMBER OF RESPONDENTS | INTERVENTION | QATQs GLOBAL RATING |
| Thomas Spencer [29] | 2005 | RTC | 6 weeks | IR-MPH | 19-60 | 146 | Patients were randomly allocated to the study or placebo group in a ratio of 2.5: 1. The study drug was titrated to 0.5 mg/kg/day until week 1, 0.75 mg/kg/day until week 2 and 1.0 mg/kg/day until week 3, at the TID dosage unless adverse effects occurred. The dose could be increased to a maximum of 1.3 mg/kg. | 2 |
| Christine Leonhard [30] | 2006 | Case Report | Not applicable | lack of information | 21 lat | Description of one patient | A 21-year-old patient was treated for the first time with methylphenidate for 19 days. The dose was titrated to 50 mg/day (patient took 30mg in the morning and 20mg in the evening). On day 20, a reversible attack occurred. | 3 |
| Joseph Biederman [31] | 2006 | RTC | 6 weeks | OROS MPH | 19-60 | 149 | Patients were randomly assigned to the study group or placebo in a ratio of 1: 1. The starting dose of the drug was 36mg and the maximum daily dose was 1.3 mg/kg. The dose was gradually increased by 36 mg/day, but only in patients who failed to achieve an a priori definition of improvement and who did not experience adverse effects. | 2 |
| Thomas J Spencer [32] | 2007 | RTC | 5 weeks | D-MPH-ER | 18-60 | 221 | Patients were equally randomised to one of four groups (d-MPH-ER 20 mg, 30 mg or 40 mg or placebo), administered once daily for 5 weeks. All started treatment with a dose of 10 mg/d, increased the dose by 10 mg/week to randomly assigned fixed doses, and then maintained at this dose for at least 2 weeks. | 1 |
| Rossella Medori [33] | 2008 | RTC | 5 weeks double-blind phase | OROS MPH | 18-65 | 401 | Patients were randomly allocated to one of four treatment groups to receive 18 mg, 36 mg or 72 mg methylphenidate or placebo once daily. Patients receiving 18 mg or 36 mg/day of methylphenidate or placebo received the treatment dose for 5 weeks. Patients in the 72 mg methylphenidate group were increased in starting dose from 36 mg/day for 4 days to 54 mg/day for 3 days, followed by 72 mg/day for 4 weeks. | 2 |
| Jan K Buitelaar [34] | 2009 | Not RTC | 7 weeks open phase | OROS MPH | 18-65 | 370 of 401 continued with the open phase of the study [5] | Patients who completed the double-blind phase [5] or discontinued treatment due to poor tolerability received a flexible dosing regimen of OROS methylphenidate flexible doses (18, 36, 54, 72 or 90 mg/day) for seven weeks. They started with a dose of 36 mg/day. Dose titration was based on clinical observations of response and tolerability. The dose could be increased by 18 mg to improve efficacy, to a maximum of 90 mg/day, or decreased by 18 mg to improve tolerability. | 2 |
| Jan K Buitelaar [35] | 2012 | RTC | 52 weeks open phase | OROS MPH | 18-65 | 155 of the 337 people who completed the study [6] | Participants in the 7-week open-label phase [6] (including those who received placebo in [5]) were eligible for the present open-label study. Patients who entered the present open-label study immediately after LAMDA continued the previous dose of OROS-MPH. Patients who discontinued the drug between the open-label phase of LAMDA and the current study started at 18 mg/d to the clinically optimal dose. Patients were maintained on a flexible dose of OROS-MPH (18, 36, 54, 72 or 90 mg/d) throughout the open-label study. The dose could be increased or decreased by 18 mg as needed to a maximum of 90 mg/d; dose changes were based on observations of clinical response and tolerability and were made entirely at the discretion of the investigator. | 1 |
| 4 weeks double-blind phase | 45 people out of 99 who completed the open phase | Patients were randomly allocated in a 1: 1 ratio to one of two groups receiving continued treatment with the same dose of OROS-MPH or placebo. |
| Michael Rösler [36] | 2009 | RTC | 24 weeks | MPH ER | 18 + | 363 | Patients were randomly assigned to MPH ER or placebo in a 2:1 ratio. The drug was titrated over the first 5 weeks to a maximum dose of 60 mg/day, starting at 10 mg/day. Lower daily doses were given for intolerable adverse events and if higher daily doses did not lead to increased improvement. The interval between two doses should be 6-8 h. The minimum maintenance dose after week 5 was 20 mg/day. | 1 |
| Markus Kraemer [37] | 2010 | Case Report | Not applicable | lack of information | 29, 38, 45 | descriptions of three patients | 3 patients treated with methylphenidate during therapy for attention deficit hyperactivity disorder experienced severe psychotic episodes. | 3 |
| Wolfgang Retz [38] | 2012 | RTC | 8 weeks | MPH ER | 18 + | 162 | For 2 weeks, patients were randomised to the optimal dose, based on tolerability and according to body weight. The maximum daily dose was 1 mg/kg body weight, starting at 10-30 mg/day. Patients were allocated to one of four weight groups (less than 55 kg, 55-69 kg, 70-104 kg and 105-130 kg) with doses of 40, 60, 80 and 120 mg per day, respectively. The interval between two doses was 6-8 h. | 1 |
| Miguel Casas [39] | 2013 | RTC | 13 weeks | OROS MPH | 18-65 | 279 | Patients were randomly assigned 1: 1: 1 to the OROS MPH 54 or 72 mg/day group or matching placebo. Patients assigned to OROS MPH started with a dose of 36 mg. From day 8, these patients received the randomly assigned dose for 12 weeks. Patients randomly assigned to placebo received placebo for 13 weeks. | 2 |
| Michael Huss [40] | 2014 | RTC | 40 weeks | MPH LA | 18-60 | 725 | Eligible patients received MPH-LA 40, 60 or 80 mg/day or matching placebo in a ratio of 1: 1: 1: 1. Treatment was started at a dose of 20 mg/day, which was increased in weekly increments of 20 mg/day until the assigned dose of 40, 60 or 80 mg was reached. The optimal dose was maintained for at least 1 week. At the last visit of the real-life dose optimisation phase, responders who still met the inclusion criteria were randomised again to enter the double-blind maintenance of effect phase at a ratio of 3:1 to their optimal dose or placebo. | 2 |
| Michael Huss [41] | 2014 | RTC | 5 weeks dose optimisation phase | MPH LA | 18-60 | 584 patients entered the open dose optimisation phase of the 725 pateints [12] | Patients who participated in the 40-week study [12] enter the dose optimisation phase. They started treatment with MPH-LA 20 mg/day up/down to an optimal dose (at which there was a balance between symptom and side effect control) of 40, 60 or 80 mg/day in 20 mg/week increments until week 12 or 13 of the ongoing study. | 1 |
| Y Ginsberg [42] | 2014 | Not RTC | 26 weeks maintenance phase | MPH LA | 18-60 | 298 patients out of 725 who started the first phase of the study [12]. | Eligible patients participating in the extension study [12,13] started treatment with MPH-LA at 20 mg and increased to optimal doses of 40, 60 or 80 mg/day in 20 mg/week increments for the first three weeks of the extension study (i.e. week 41-43 of the study). The investigator had the flexibility to adjust doses as necessary (between weeks 44 and 66), as long as the dose remained in the MPH-LA range of 40-80 mg/day. | 3 |
| Nagahide Takahashi [43] | 2014 | RTC | 8 weeks | OROS MPH | 18-64 | 284 | Eligible patients were randomly allocated in a 1: 1 ratio to the group receiving OROS MPH or placebo. Initially, patients received OROS MPH 18 mg/day or placebo for the first week. The dose was then increased by 18 mg over the following weeks to a maximum dose of 72 mg/day until an individually optimised dose was achieved. If necessary for safety reasons, the dose could be reduced by 18 mg once during the dose adjustment period by the investigator. Once the patient's dose was reduced, it could not be increased thereafter. | 1 |
| Muhammad Muzaffar Mahmood [44] | 2016 | Case Report | Not Applicable | lack of information | 30 | One patient's description. | A 30-year-old patient was hospitalised for acute anterior ST-segment elevation myocardial infarction. Coronary angiography did not show any coronary artery obstruction, and coronary artery spasm was proposed as the likely mechanism of AMI, and could be caused by methylphenidate. The patient received antiplatelet therapy with statins, beta-blockers and ACE-I therapy, and methylphenidate therapy was stopped. | 3 |
| David W Goodman [45] | 2017 | RTC | 6 weeks | OROS MPH | 18-65 | 357 | Subjects were randomly allocated to the 18 mg/d OROS methylphenidate treatment group or matching placebo. The treatment dose could be increased at each of 3 consecutive weekly visits to 36 mg, 54 mg and 72 mg (maximum) until the patient reached an AISRS score < 18 or the tolerance limit. | 2 |
| Elliyeh Ghadrdan [46] | 2018 | Case Report | Not applicable | lack of information | 65 | description of one patient | This case presents psychotic symptoms caused by methylphenidate in a 65-year-old woman who was taking this medication for ADHD. She had been taking three to four methylphenidate hydrochloride tablets daily for several months and thought they were sleeping pills. | 3 |
| Margaret D Weiss [47] | 2021 | RTC | 4 weeks double-blinde phase | PRC-063 | 18+ | 375 | Eligible participants were randomly allocated in a 1: 1: 1: 1: 1 ratio to receive 25, 45, 70 or 100 mg/day of PRC-063 or matching placebo. Participants randomised to the higher dose groups increased the dose of PRC-063 each week until the randomised dose was reached. Participants not enrolled in the open label study completed a 14-day safety observation. | 1 |
| 6 months open phase | 184 patients out of 375 who started phase one. | Participants started on the investigator-specified daily dose of PRC-063 on the day following the end of the double-blinde study, regardless of whether the participant had previously received active treatment or placebo. Seven doses of PRC-063 were available in the OL study: 25, 35, 45, 55, 70, 85 and 100 mg/day. |